Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry

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Complete List of Authors:	Mazieres, J.; Toulouse universitary hospital, Hôpital larrey, Thoracic oncology Drilon, Alexander; Memorial Sloan Kettering Cancer Center, Thoracic Oncology Service, Division of Solid Tumor Oncology, Department of Medicine Lusque, Amelie; Institut Universitaire du Cancer Toulouse Oncopole, Biostatistics unit, Institut Claudius Regaud Mhanna, Laurent; Toulouse universitary hospital, Hôpital larrey, Thoracic oncology Cortot, Alexis; Lille University Hospital, Respiratory Diseases and Thoracic Oncology Department Mezquita, Laura; Gustave Roussy, Medical Oncology Department Thai, Alesha; Peter MacCallum Cancer Centre, Medical Oncology Mascaux, Celine; Assistance Publique Hopitaux de Marseille, Multidisciplinary Oncology and Therapeutic Innovation Department Couraud, Sébastien; Hospices Civils de Lyon, CH Lyon Sud, Service de pneumologie et oncologie thoracique; Université Lyon 1, Faculté de médecine et de maïeutique Lyon Sud Veillon, Rémy; Centre Hospitalier Universitaire de Bordeaux, Respiratory Department van den heuvel, Michel; Radboudumc Instituut voor Wetenschappelijk Onderwijs en Opleidingen, Pulmonology Neal, Joel; Stanford Cancer Institute, Medical Oncology Peled, Nir; Soroka University Medical Center, oncology Früh, martin; Oncology and Hematology, Kantonsspital St. Gallen Ng, Terry; University of Colorado at Denver - Anschutz Medical Campus, Division of Medical Oncology Gounant, Valérie; Hopital Bichat - Claude-Bernard, Thoracic Oncology Department

	Popat, Sanjay; The Royal Marsden Hospital, Surrey, Breast Unit Diebold, Joachim; Luzerner Kantonsspital, Institute of Pathology Sabari, Joshua ; Memorial Sloan Kettering Cancer Center, Medicine Zhu, Viola; University of California, Irvine, Medicine Rothschild, Sacha; University Hospital Basel, Medical Oncology Bironzo, Paolo; University of Turin, Department of Oncology; San Luigi Gonzaga Hospital, Division of Medical Oncology Martinez, Alex; Vall d´Hebron University Hospital, Medical Oncology Service Curioni-Fontecedro, Alessandra; Univerisity Hospital Zurich, Hematology and Oncology Rosell, Rafael; Catalan Institute of Oncology, Director, Cancer Biology and Precision Medicine Program Lattuca-Truc, Mickael; Grenoble Universitary Hospital, Pulmonology Wiesweg, Marcel; West German Cancer Center, University Hospital Essen, University Duisburg-Essen, Department of Medical Oncology Besse, Benjamin; Gustave Roussy, Medical Oncology Department Solomon, Benjamin; Peter MacCallum Cancer Centre, Medical Oncology Barlesi, Fabrice; Aix Marseille University, CRCM, AP-HM, Multidisciplinary Oncology & Therapeutic Innovations Schouten, Robert; Radboudumc Instituut voor Wetenschappelijk Onderwijs en Opleidingen, Pulmonology Wakelee, Heather; Stanford Comprehensive Cancer Center, Medical oncology; Camidge, Ross; University of Colorado Cancer Center, Medicine/oncology Zalcman, Gérard; Hopital Bichat - Claude-Bernard, Thoracic Oncology Department Novello, Silvia; University of Turin, Department of Clinical & Biological Sciences Ou, Ignatius; University of California, Irvine, Medicine Milia, Julie; Toulouse universitary hospital, Hôpital larrey, Thoracic Oncology Gautschi, Oliver; Medical Oncology, Internal Medicine
Keywords:	Immunotherapy, lung cancer, oncogenic addiction
Abstract:	Background: Anti-PD1/PD-L1 directed immune-checkpoint-inhibitors (ICI) are widely used to treat patients with advanced non-small cell lung cancer (NSCLC). The activity of ICI across NSCLC harboring oncogenic alterations is poorly characterized. The aim of our study was to address the efficacy of ICI in the context of oncogenic addiction. Patients and methods:We conducted a retrospective study for patients receiving ICI monotherapy for advanced NSCLC with at least one oncogenic driver alteration. Anonymized data were evaluated for clinicopathologic characteristics and outcomes for ICI therapy: best response (RECIST 1.1), progression-free survival (PFS) and overall survival (OS) from ICI initiation.The primary endpoint was PFS under ICI. Secondary endpoints were best response (RECIST 1.1) and overall survival (OS) from ICI initiation. Results: We studied 551 patients treated in 24 centers from 10 countries. The molecular alterations involved KRAS (n=271), EGFR (n=125), BRAF (n=43), MET (n=36), HER2 (n=29), ALK (n=23), RET (n=16), ROS1 (n=7), and multiple drivers (n=1). Median age was 60 years, gender-ratio was 1:1, never/former/current smokers were 28/51/21% respectively, and the majority of tumors were adenocarcinoma. The objective response rate by driver alteration was: KRAS=26%, BRAF=24%, ROS1=17%, MET=16%, EGFR=12%, HER2=7%, RET=6%, ALK=0%. In the entire cohort, median PFS was 2.8 months, OS 13.3 months and the best response rate 19%. In a subgroup analysis, median PFS (in months) was 2.1 for EGFR, 3.2 for KRAS, 2.5 for ALK, 3.1 for BRAF, 2.5 for HER2, 2.1 for RET, and 3.4 for MET. In certain subgroups, PFS was positively associated with PD-L1 expression

	(KRAS, EGFR) and with smoking status (BRAF, HER2). Conclusions:ICI induced regression in some tumors with actionable driver alterations, but clinical activity was lower compared to the KRAS group and the lack of response in the ALK group was notable. Patients with actionable tumor alterations should receive targeted therapies and chemotherapy before considering immunotherapy.

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Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry

J. Mazières[1], A. Drilon[2], A. Lusque[3], L. Mhanna[1], A.B. Cortot[4], L. Mezquita[5], A.A. Thai [6], C. Mascaux[7], S. Couraud[8], R. Veillon[9], M. Van Den Heuvel[10], J. Neal[11], N. Peled[12], M. Früh[13], T. L. Ng[14], V. Gounant[15], S. Popat[16], J. Diebold[17], J. Sabari[2], V.W. Zhu[18], S.I. Rothschild[19], P. Bironzo[20], A. Martinez[21], A. Curioni-Fontecedro[22], R. Rosell[23], M. Lattuca-Truc[24], M. Wiesweg[25], B. Besse[5], B. Solomon[6], F. Barlesi[7], R.D. Schouten [10], H. Wakelee[11], D.R. Camidge[14], G. Zalcman[15], S. Novello[20], S. I. Ou[18], J. Milia[1], O. Gautschi [26].

[1] Thoracic Oncology Department, Toulouse University Hospital, Université Paul Sabatier, Toulouse, France

[2] Early Drug Development service, Memorial Sloan Kettering Cancer Center, New York, United States.

[3] Biostatistics Unit, Institut Claudius Regaud, IUCT-O, Toulouse, France

[4] Thoracic Oncology Department, Lille Universitary hospital, Lille University, Lille, France.

[5] Medical oncology department, Institut d'Oncologie Thoracique, Institut Gustave Roussy, Villejuif, France.

[6] Medical Oncology department, Peter MacCallum Cancer Institute, Melbourne, Australia.

[7] Multidisciplinary Oncology and Therapeutic Innovations Department, Assistance Publique Hôpitaux de Marseille, Aix Marseille University, CNRS, INSERM, CRCM, Marseille, France.

[8] Respiratory diseases and thoracic oncology department, Lyon Sud Hospital, Cancer Institute of Hospices Civils de Lyon, Lyon 1 University, France.

[9] Pulmonology Department, Bordeaux University Hospital, Pessac, France.

[10] Faculty of medical science, Radboud university medical center, Nijmegen, the Netherlands.

[11] Division of Oncology, Department of Medicine. Stanford Cancer Institute/Stanford University. Stanford, CA, USA.

[12] Soroka Medical Center & Ben-Gurion University, Beer-Sheva, Israel.

[13] Department of Oncology, Haematology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland.

[14] Thoracic Oncology Department, University of Colorado Cancer Center, Aurora, Colorado, USA.

[15] Department of Thoracic Oncology, Paris-Nord, Bichat-Claude Bernard Hospital, APHP, Paris, France.

[16] Royal Marsden Hospital, London, United Kingdom.

[17] Pathology Department, University of Bern and Cantonal Hospital, Luzern, Switzerland.

[18] Department of Medicine, Division of Hematology-Oncology, University of California Irvine School of Medicine, Orange, CA, USA.

[19] Department Internal Medicine, University Hospital Basel, Medical Oncology, Basel, Switzerland.

[20] Department of Oncology, University of Torino, Torino, Italy.

[21] Medical Oncology Department, Vall d'Hebron Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain.

[22] Center of Hematology and Oncology University Hospital Zurich, Switzerland.

[23] Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Badalona, Spain; Germans Trias i Pujol Research Institute (IGTP), Badalona, Spain

[24] Pulmonology department, Grenoble universitary hospital, Grenoble, France.

[25] Department of Medical Oncology, West German Cancer Center, University Hospital Essen, University Duisburg-Essen, Germany.

[26] Oncology Department, University of Bern and Cantonal Hospital, Luzern, Switzerland.

CORRESPONDING AUTHOR

Prof Julien Mazières,

Thoracic Oncology Department

Hôpital LARREY

CHU Toulouse
24 Chemin de Pouvourville
31059 TOULOUSE
FRANCE
Tel: +33 567 771 837
Fax: +33 567 771 486
Email: mazieres.j@chu-toulouse.fr

Abstract:

Background: Anti-PD1/PD-L1 directed immune-checkpoint-inhibitors (ICI) are widely used to treat patients with advanced non-small cell lung cancer (NSCLC). The activity of ICI across NSCLC harboring oncogenic alterations is poorly characterized. The aim of our study was to address the efficacy of ICI in the context of oncogenic addiction.

Patients and methods: We conducted a retrospective study for patients receiving ICI monotherapy for advanced NSCLC with at least one oncogenic driver alteration. Anonymized data were evaluated for clinicopathologic characteristics and outcomes for ICI therapy: best response (RECIST 1.1), progression-free survival (PFS) and overall survival (OS) from ICI initiation. **The primary endpoint was** PFS **under ICI. Secondary endpoints were** best response (RECIST 1.1) and overall survival (OS) from ICI initiation.

Results: We studied 551 patients treated in 24 centers from 10 countries. The molecular alterations involved *KRAS* (n=271), *EGFR* (n=125), *BRAF* (n=43), *MET* (n=36), *HER2* (n=29), *ALK* (n=23), *RET* (n=16), *ROS1* (n=7), and multiple drivers (n=1). Median age was 60 years, gender-ratio was 1:1, never/former/current smokers were 28/51/21% respectively, and the majority of tumors were adenocarcinoma. The objective response rate by driver alteration was: *KRAS*=26%, *BRAF*=24%, *ROS1*=17%, *MET*=16%, *EGFR*=12%, *HER2*=7%, *RET*=6%, *ALK*=0%. In the entire cohort, median PFS was 2.8 months, OS 13.3 months and the best response rate 19%. In a subgroup analysis, median PFS (in months) was 2.1 for *EGFR*, 3.2 for *KRAS*, 2.5 for *ALK*, 3.1 for *BRAF*, 2.5 for *HER2*, 2.1 for *RET,* and 3.4 for *MET*. In certain subgroups, PFS was positively associated with PD-L1 expression (*KRAS*, *EGFR*) and with smoking status (*BRAF*, *HER2*).

Conclusions: ICI induced regression in some tumors with actionable driver alterations, but clinical activity was lower compared to the *KRAS* group and the lack of response in the ALK group was notable. Patients with actionable tumor alterations should receive targeted therapies and chemotherapy before considering immunotherapy.

Key words: Immunotherapy-lung cancer-oncogenic addiction

Key message:

Question: Is Immunotherapy efficient in patients with lung cancer and harboring an oncogenic addiction?

Findings: Patients' outcome treated with ICI monotherapy were consistent with ICI registration trials in the KRAS-subgroup but were inferior for patients with actionable driver mutations.

Meaning: ICI should thus only be considered after exhaustion of targeted and standard therapies.

Introduction

The management of patients with stage 4 non-small cell lung cancer (NSCLC) is currently undergoing significant transformation. Molecular testing, targeted therapies and immunotherapy are now part of routine clinical care [1]. Targeted therapies are efficient in the context of oncogenic driver mutations [2]. These treatments are usually associated with high response rate, but also with unavoidable development of resistance and tumor recurrence [3]. Therapeutic options are restrained in patients after exhaustion of targeted therapies and chemotherapy. Immune checkpoint inhibitors (ICI) which block the Programmed Death-1 (PD-1) /Programmed Death Ligand 1 (PD-L1) axis are a new standard of care not only in pretreated patients, but also in the first line setting [4-6]. ICI response rates in general are approximately 20% in unselected NSCLC, but overall survival benefit was well documented in registration trials [7-10].

Whether ICIs alone or even in combination with TKIs would offer comparable benefit in oncogene addicted subtypes of NSCLC as much as in the general unselected NSCLC population has been raised as a relevant question [11]. We may expect that immunotherapy may transform the important tumor responses achieved with targeted inhibitors in prolonged remissions. Nevertheless, data obtained from subgroups in clinical trials [9,10,12] and from investigators observations have shown rather weak activity of ICI in NSCLC patients harboring actionable driver mutations [13]. Many arguments have been proposed including low immunogenicity of tumors with single oncogenic addiction, inconstant PD-L1 expression, high proportion of never-smokers in this population, or low tumor mutational burden [11]. Therefore, the optimal use of ICI therapy in patients with actionable driver mutations remains an important field of ongoing research.

The purpose of this study was to analyze the clinical activity of ICI therapy in the context of oncogenic driver alterations. We previously conducted registry studies on targeted therapies for NSCLC with *ROS1*, *HER2*, *BRAF* and *RET* alterations [14-18]. We used our established network to perform a wide international cohort of patients with molecularly defined NSCLC. Hereinafter, we present the results for the whole cohort, and for individual molecular subgroups.

Patients and methods

Study objectives.

The primary objective of our study was to describe the progression-free survival (PFS) of patients treated with PD1/PD-L1 checkpoint inhibitors (ICI) in each subgroup carrying a molecular abnormality, namely *EGFR*, *ALK*, *ROS1*, *HER2*, *BRAF*, *MET*, *RET* and *KRAS*. The secondary objectives were both the best overall response (that was not confirmed by a second measurement) and the overall survival for each molecular subgroup. We also analyzed the outcome of patients according to smoking status, line of treatment, and PD-L1 expression.

Patients' selection

A global multicenter network of thoracic oncologists accrued patients in this registry. Investigators were identified via an ongoing collaboration established by our prior registries [14-18]. Eligible patients had 1) a pathological diagnosis of lung cancer according to IASLC/OMS classification; 2) local testing positive (either direct sequencing or NGS on validated platforms) for at least one oncogenic driver mutation: *EGFR* (exon 18-21) activating mutation, *HER2 (exon 20)* activating mutation, *KRAS* mutation, *BRAF* (exon 15) mutation, *MET* amplification or exon 14 mutation, *ALK* rearrangement, *ROS1* rearrangement or *RET* rearrangement; 3) single agent ICI therapy with commercial anti-PD1/PD-L1-antibodies; 4) local response assessment according to RECIST1.1 criteria; 5) follow-up with survival status. Optionally, investigators were asked to record immunotherapy-related adverse events (irAE), and PD-L1 expression in tumor cells through local immunohistochemistry tests.

PD-L1 analysis

PD-L1 analysis was performed in each center according to local procedures. Antibodies used were E1L3N (32.8%), SP142 (31.7%), 22C3 (22.2%), SP263 (6.7%), 28-8 (5.6%), and others (1.1%). Results were provided in percentage of staining of tumor cells with 3 cut-off levels: 1%, 10% and 50%.

Ethical considerations

The study was approved by the national ethics committees of France (CEPRO 2017-043, CNIL Nh22181405l) and Switzerland (Swissethics/EKNZ ID 2017-01530). Participating centers were responsible for patients' consent and institutional approval. All contributors were trained in Good Clinical Practice. The study was a purely

academic collaboration granted by both Toulouse and Lucerne Hospitals and was not funded by industry.

Data collection and response assessment

Anonymized clinical data were recorded by local investigators using electronic case report forms (eCRF) in a password-protected secure online portal from the University of Toulouse [https://ec.claudiusregaud.fr/CSOnline/]. Data were centrally collected at the University of Toulouse (France). The registry was open for enrolment from May 2017 until April 2018. Best response to systemic therapies, defined as a complete or partial response achieved at least once during the course of therapy, was assessed locally using RECIST v1.1 criteria. Patients treated in clinical trials were not included in our study.

Statistical methods

All statistical evaluations were performed by the trial statistician (AL), according to the predefined plan as stated in the protocol. Data were summarized according to frequency and percentage for qualitative variables, and by median and range for quantitative variables. The 95% confidence interval for response rate was calculated using the exact binomial distribution. PFS was measured as the time from the first administration of ICI therapy to progression defined by RECIST1.1, or death due to any cause. Patients alive without progression at the time of analysis were censored at the initiation of a new therapy or last follow-up. Overall survival was measured as the time from the first administration of ICI therapy to death due to any cause. Patients alive at the time of analysis were censored at the last follow-up. Survival data were estimated using the Kaplan–Meier method and compared using the log-rank test in overall cohort and oncogenic driver subgroups. Statistical analyses were carried out using STATA 13.1 software (StataCorp, TX, USA).

Results

Patients' characteristics

During an enrolment phase of almost one year, the registry included 551 patients from 24 centers in 10 countries. The molecular alterations involved *KRAS* (n=271), *EGFR* (n=125), *BRAF* (n= 43, *V600E* n=17, other n=18), *MET* (n=36, *MET* amplification n=13, exon 14 skipping mutation n=23), *HER2* (n=29), *ALK* (n=23), *RET* (n=16), *ROS1* (n=7).

34 patients with more than one driver were allocated to the dominant oncogenic driver. Details are provided in the supplementary data (S1:CONSORT diagram and S2). Median age was 60 years (range: 29-83). Gender-ratio was 1:1. Smoking status was 28% never-smokers, 51% former smokers, and 21% current smokers. The majority (96%) of tumors were adenocarcinoma. At the time of immunotherapy initiation, most patients had ECOG Performance Status (PS) of 1 (64%), while fewer patients were PS0 (21%), PS2 (11%), and PS3/4 (4%). All patients presented an advanced tumor stage at the beginning of immunotherapy. The clinical characteristics of each subgroup are reported in Table 1.

Treatment characteristics and safety

Most (94%) patients received anti-PD1-antibodies (nivolumab n = 466, pembrolizumab n = 48, other n = 6), fewer patients (6%) had anti-PD-L1-antibodies (atezolizumab n = 19, durvalumab n = 11, other n = 1). ICIs were given in the first (5%), second (41%), third (26%), fourth line (13%) or in later lines (14%) of treatment (S3). The recording of significant (grade 3-4) immunotherapy-related adverse events (irAE) was optional. From 462 patients with available data, 50 (10.8%) had grade 3-5 irAEs, including 36 (7.8%) of grade 3, 13 (2.8%) of grade 4 and 1 of grade 5 (0.2%, endocrine disorder). The pneumonitis rate was in the expected range (13 cases, 2.8% including 8 grade 3 and 5 grade 4). No unexpected irAEs were recorded.

PD-L1 expression

PD-L1 status determined by immunohistochemistry was available for 214 patients. The median number of positive cells was 10%. Using a 1% cut-off, one third were negative (33.2%) and two-third positive (66.8%). Using a 10% cut-off, half of the tumors was negative (49.7%) and half positive (50.3%). Using a 50% cut-off, one-third of the tumors was positive (33.9%). Looking into each subgroup, we found that median percentage of cells expressing PD-L1 was 0 in *HER2* (n= 13), 3.5 in *EGFR* (n=38), 7.5 in *ALK* (n=10), 12.5 in *KRAS* (n=80), 26 in *RET* (n=6), 30 in *MET* (n=15), 50 in *BRAF* (n=9) and 90 in *ROS1* (n=5) subgroups. S4 and S5.

Clinical outcomes

Response rate

Responses were not confirmed by a second measurement. The rate of any partial or complete response was 19% [95%CI: 16-23%], ranging from 0% in ALK patients to 26% in KRAS mutated patients. If we consider the KRAS patients as a control group and exclude them from the analysis, the best response rate for patients harboring all other molecular alterations was 12.7%. We then classified the subgroups according to the rate of progressive disease. Progressive disease (PD) was observed in 46% for *BRAF*, 50% for *MET*, 51% for *KRAS*, 67% for *HER2*, 67% for *EGFR*, 68% for *ALK*, 75% for *RET* and 83% for *ROS1*. Fig. 1, S6.

Overall survival

In the entire cohort, median follow-up was 16.1 months, and median OS from start of ICI therapy was 13.3 months [10.0-14.9] (Fig. 2). Median OS (in months) for individual molecular subgroups was 10.0 [6.7;14.2] for *EGFR* mutated patients, 13.5 [9.4;15.6] for *KRAS*, 17.0 [3.6;NR] for *ALK*, 13.6 [7.4;22.5] for *BRAF*, 20.3 [7.8;NR] for *HER2*, 21.3 [3.8;28.0] for *RET* and 18.4 [7.0;NR] for *METS7*. In the univariate analysis, OS did not correlate with gender, age, smoking, number of prior therapies, or PD-L1 expression (S8).

Progression-free survival

In the entire cohort, median PFS was 2.8 months [95%IC 2.5-3.1]. Median PFS (in months) for individual molecular subgroups was 2.1 [1.8;2.7] for *EGFR*, 3.2 [2.7;4.5] for *KRAS*, 2.5 [1.5;3.7] for *ALK*, 3.1 [1.8;4.6] for *BRAF*, 2.5 [1.8;3.5] for *HER2*, 2.1 [1.3;4.7] for *RET* and 3.4 [1.7;6.2] for *MET* (Fig. 2). Long-term responders were more frequent in *KRAS* (12-months PFS: 25.6 %), *MET* (23.4%) and *BRAF* (18.0%) subgroups, than in *EGFR* (6.4%), *ALK* (5.9%), *HER2* (13.6%) and *RET* (7.0%) subgroups (Table 2). If we exclude KRAS patients from the analysis (n=279 patients with all other alterations), median PFS was 2.4 months.

In the univariate analysis, PFS significantly correlated with smoking (median PFS: 2.5, 2.8 and 3.5 months for never smokers, former smokers and current smokers, respectively, $p < 0.0001$), and with PD-L1 expression (3.0 *vs* 4.2 months for negative and positive expression of PD-L1, $p = 0.02$). However, PFS did not correlate with gender ($p = 0.5$), age ($p = 0.3$) or number of previous lines of treatment ($p = 0.08$). (S9 and S10). Interestingly, a higher rate of rapid progression (within 2 months) was observed for EGFR (44.8%), ALK (45.5%), ROS1 (42.9%) and RET (43.8%) patients than for KRAS (36%) (S11) respectively.

Molecular subgroup analyses

KRAS mutations were identified in 271 patients. PFS was not significantly different regarding *KRAS* mutation subtype if we compare *G12C* (n = 100) to other mutations (n = 143, *p* = 0.47) or *G12D* (n = 39) *vs* other *KRAS* mutations (n = 204, *p* = 0.40). PFS did also not correlate with smoking (*p* = 0.98), or with the number of previous lines of treatment. In patients with available PD-L1 expression data (n = 95), PD-L1 positive expression was significantly (*p* = 0.01) correlated with a longer PFS (median PFS: 7.2 vs 3.9 months) (Fig 3). We also separate patients harbouring KRAS transition (G12D, G13D, G12S) from KRAS transversion (G12C, G12A, G12V, G13C). PFS was not impacted by the nature of KRas alteration (2.9 months for transition, 4.0 for transversion, p = 0.27, (S12).

EGFR mutations were reported in 125 patients. PFS was significantly different across molecular subgroups ranging from 1.4 month in *T790M* and complex mutations subgroup to 1.8 for exon 19, 2.5 for exon 21 and 2.8 for other mutations (*p* < 0.001). PFS correlated neither with smoking (*p* = 0.06), nor with the number of previous lines of treatment. PD-L1 positivity was significantly correlated with a longer PFS (2.8 months *vs.* 1.7, p=0.01) (Fig 3).

BRAF mutations were identified in 43 patients. PFS was significantly higher in smokers *vs.* never smokers (4.1 *vs.* 1.9 months, *p* = 0.03). Median PFS was numerically shorter in the V600E subgroup (1.8 months) compared to other *BRAF* mutations (4.1 months) but this difference did not reach significance (*p* = 0.20).

MET molecular alterations were found in 36 patients. Median PFS correlated neither with alteration subtype (exon 14 skipping mutation *vs* other MET alterations including MET amplification, *p* = 0.09), nor with smoking.

HER2 mutations were identified in 29 patients. PFS correlated with smoking (3.4 months for smokers *vs* 2.0 months for never smokers, *p* = 0.04).

Due to a low number of patients, *ALK*, *ROS1* and *RET* were analyzed together in a subgroup termed “rearrangements”. Median PFS was only slightly higher in never-smokers (2.6 months) than in smokers (1.8 months, *p* = 0.03). PD-L1 was not available in enough patients but no tumor response was reported in patients from this group in the context of PD-L1 positivity. (S13, S5). Main results for all cohorts are presented in S14.

Discussion

The standard of care for patients with actionable driver alterations (*EGFR*, *ALK*, *ROS1* and *BRAF-V600E*) is a targeted therapy. A targeted therapy should also be considered for *HER2 [16]*, *RET [17],* and *MET* alterations. After exhaustion of targeted agents and chemotherapy, immunotherapy may be considered as a salvage treatment. Nevertheless, evidence to support the role of ICI in this setting is controversial, as *EGFR* and *ALK* alterations have been associated with low ICI efficacy in prior studies [19]. To address this issue, we conducted a global "real world" study. Our study was retrospective and had other limitations, including reporting bias, lack of central molecular and radiologic assessment, and variable scanning intervals. Nevertheless, we obtained new findings of clinical relevance.

In the overall cohort, the best response with ICI therapy by RECIST was 19%, and median PFS was 2.8 months. This result was mainly driven by the large KRAS subgroup, and it is in concordance with registration trials testing immunotherapy in pretreated patients, regardless *EGFR* or *ALK* status [9] [10]. Regarding molecular subgroups, we confirmed that patients with *KRAS*-mutant NSCLC derived a greater benefit from ICI than *EGFR*-mutant NSCLC, as reported in the previous Checkmate-057 trial [9]. It has been reported that *KRAS*-mutant NSCLC are more likely to express PD-1 and PD-L1[20]. Calles *et al.* also showed that *KRAS* mutant tumors were more likely to express PD-L1 when the patient was a smoker [21]. In a recent study, Falk *et al.* found that *KRAS*-mutant tumor cells significantly express more PD-L1 than KRAS-WT cells. Interestingly, the distribution of PD-L1 expression in tumor cells was significantly related to the subtype of mutant *KRAS*, with tumors expressing the *G12V* substitution harboring a higher expression of PD-L1 [22]. In our study, we have not been able to detect a significant correlation between KRAS mutation subtypes and PFS, but we confirmed that PD-L1 expression is associated with a better outcome. Recently, *STK11/LKB1* co-mutation in KRAS-mutant NSCLC was reported as a new predictive marker for tumor resistance to ICI therapy [23]. *STK11* was not part of routine testing and our study did not include tissue collection, therefore, future studies will have to validate this interesting finding in a larger cohort. ICI are thus an adequate treatment for *KRAS* mutated patients and markers including PD-L1 may identify the best candidates in a better way. Nevertheless, the limited number of patients with available PDL1 status and the heterogeneity of the tests did not allow us to draw a definitive conclusion on its potential interest.

Interestingly, if we exclude KRAS patients from our analysis and focus only on targetable drivers, the outcome is lower with 12.7% response rate and 2.4 months PFS. Recent studies showed an inverse relationship between PD-L1 expression and EGFR mutations and no association between PD-L1 expression and ALK rearrangement was reported. Moreover, an uninflamed tumor microenvironment is often reported in the context of oncogenic addiction [24,25]. Gainor *et al.* also suggested that a dearth of tumor-infiltrating $CD8^+$ lymphocytes, may explain the low response rate to PD-1 axis inhibitors observed amongst EGFR- and ALK-driven NSCLC [26].

Concerning patients with *EGFR* mutation, the role of ICI therapy is still controversial. Murine models have shown that PD-L1 can be overexpressed in the context of *EGFR* mutation, and significant response has been reported to anti-PD1-antibodies in preclinical studies [27]. In a retrospective study, Gainor *et al.* identified a very low response rate in patients with *EGFR*-mutant NSCLC treated with ICI-therapy (1 of 28, 3.6%) [13]. A recent meta-analysis including 3 randomized trials of immunotherapy in TKI-pretreated patients reported that ICI do not improve OS compared to docetaxel in patients *with EGFR*-mutant NSCLC [28]. In addition, a recent phase II trial of pembrolizumab in TKI-naive patients with PD-L1 positive *EGFR*-mutant NSCLC showed no RECIST responses in the first 11 patients and the trial was stopped [29]. In the phase II trial ATLANTIC of durvalumab in EGFR/ALK mutant NSCLC, response rate was 3.6% for PD-L1 < 25%, and 12.2% for PD-L1 > 25%. Median PFS was 1.9 month [19]. We found similar outcomes in our cohort, with a 12% RR and 2.1 months PFS. Together, these results support the use of PD-L1 for decision making regarding ICI therapy in TKI-pretreated patients with EGFR-mutant NSCLC, although even with higher levels of expression, response rates remain low compared to targeted therapy [29]. Benefit has, however, been reported in patients with EGFR mutations with the combination of carboplatin, paclitaxel, bevacizumab and atezolizumab in the IMpower150 trial [5].

BRAF mutations were associated with slightly better outcomes compared to *EGFR* mutations (RR 24% and PFS 3.1 months). The potential efficacy of immunotherapy in *BRAF* mutant melanoma has already been suggested [30]. It has been shown in melanoma that BRAF inhibition has favorable effects in the tumor microenvironment [31]. Recently, Dudnik et al. reported frequent expression of PDL1 and comparable

PFS (3.7 months) in BRAF V600E mutated patients [32]. In our study, PFS in patients with *BRAF*-mutant NSCLC was positively associated with smoking status. It thus appears that immunotherapy may be considered in *BRAF* positive patients after targeted therapy and one line of chemotherapy.

Our MET altered cohort contained several different potential subgroups, while MET exon 14 skip mutations may be most clearly defined, the other category, which included both MET amplification at various levels may or may not represent true oncogene-addicted states [33]. ICI activity in MET exon 14 has recently been reported to be very low even in the setting of high TMB or high PD-L1 [34]. Of note, amongst the 5 responses seen to ICI in the MET cohort these occurred only in 2 patients with exon 14 skipping mutations.

ALK, *ROS1* and *RET* translocation represent a small subgroup of NSCLC. Nevertheless, several cases were included in our study. PD-L1 expression was relatively high in those cases. However, most tumors were refractory to ICI therapy. These observations were consistent with other studies, namely with ATLANTIC for ALK, and with a cohort study from MSKCC for RET [34]. Moreover, only one ROS1 patients responded, the remaining 6 patients progressed through first CT-scan. Although these data are preliminary, we do not recommend ICI as single agents in patients with ALK/ROS1/RET rearranged NSCLC. Further studies are requested to see if patients may do better with combination therapies, as suggested for EGFR [5].

In conclusion, patients' outcome treated with ICI monotherapy overall were consistent with ICI registration trials, based on the large KRAS-subgroup in our study. However, outcomes for patients with actionable driver mutations (EGFR, ALK, ROS1) were inferior and ICI should only be considered after exhaustion of targeted therapies and in some cases, potentially in all other therapies including standard and salvage chemotherapies. Indeed in the case of ALK+ disease, our data, now added to several others, demonstrate that not a single ALK+ NSCLC case has had a documented response to monotherapy from ICI [13,19] . We think that there are two ways to optimize the use of immunotherapy in the context of oncogenic addiction. The first one is to combine immunotherapy with other drugs such as chemotherapy and anti-angiogenic agents. The second one is to identify new relevant biomarkers besides PD-L1 expression and TMB considering the complex molecular biology of NSCLC.

NOTE

Preliminary results were presented at the ASCO-SITC meeting (2018 January 26th, San Francisco, abstract #172) and at the ASCO Annual Meeting, (2018 June 1st, abstract #9010, oral communication in Clinical Science Symposium).

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BIBLIOGRAPHY

1. Doroshow DB, Herbst RS. Treatment of Advanced Non-Small Cell Lung Cancer in 2018. JAMA Oncol 2018; 4: 569-570.
2. Resources NGC. NCCN Framework for Resource Stratification of NCCN Guidelines (NCCN Framework™). In NCCN Guidelines® & Clinical Resources. https://www.nccn.org/framework/ 2019.
3. Cortot AB, Janne PA. Molecular mechanisms of resistance in epidermal growth factor receptor-mutant lung adenocarcinomas. Eur Respir Rev 2014; 23: 356-366.
4. Reck M, Rodriguez-Abreu D, Robinson AG et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016; 375: 1823-1833.
5. Socinski MA, Jotte RM, Cappuzzo F et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N Engl J Med 2018; 378: 2288-2301.
6. Gandhi L, Rodriguez-Abreu D, Gadgeel S et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med 2018; 378: 2078-2092.
7. Brahmer J, Reckamp KL, Baas P et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. New England Journal of Medicine 2015; 373: 123-135.
8. Borghaei H, Brahmer J. Nivolumab in Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 2016; 374: 493-494.
9. Borghaei H, Paz-Ares L, Horn L et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. New England Journal of Medicine 2015; 373: 1627-1639.
10. Herbst RS, Baas P, Kim DW 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: 1540-1550.
11. Gettinger S, Politi K. PD-1 Axis Inhibitors in EGFR- and ALK-Driven Lung Cancer: Lost Cause? Clin Cancer Res 2016; 22: 4539-4541.
12. Fehrenbacher L, Spira A, Ballinger M 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: 1837-1846.
13. Naidoo J, Schindler K, Querfeld C et al. Autoimmune Bullous Skin Disorders with Immune Checkpoint Inhibitors Targeting PD-1 and PD-L1. Cancer Immunol Res 2016; 4: 383-389.
14. Gautschi O, Bluthgen MV, Smit E et al. Targeted therapy for BRAF-mutant lung cancer: Results from the European EURAF cohort study In ELCC. Geneva: 2015.
15. Mazieres J, Zalcman G, Crino L et al. Crizotinib therapy for advanced lung adenocarcinoma and a ROS1 rearrangement: results from the EUROS1 cohort. Journal of Clinical Oncology 2015; 33: 992-999.
16. Mazieres J, Barlesi F, Filleron T et al. Lung cancer patients with HER2 mutations treated with chemotherapy and HER2-targeted drugs: results from the European EUHER2 cohort. Annals of Oncology 2015.
17. Gautschi O, Milia J, Filleron T et al. Targeting RET in Patients With RET-Rearranged Lung Cancers: Results From the Global, Multicenter RET Registry. J Clin Oncol 2017; 35: 1403-1410.
18. Mazieres J, Peters S, Lepage B et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. J Clin Oncol 2013; 31: 1997-2003.
19. Garassino MC, Cho BC, Kim JH et al. Durvalumab as third-line or later treatment for advanced non-small-cell lung cancer (ATLANTIC): an open-label, single-arm, phase 2 study. Lancet Oncol 2018; 19: 521-536.
20. Chen N, Fang W, Lin Z et al. KRAS mutation-induced upregulation of PD-L1 mediates immune escape in human lung adenocarcinoma. Cancer Immunol Immunother 2017; 66: 1175-1187.
21. Khunger M, Rakshit S, Pasupuleti V et al. Incidence of Pneumonitis With Use of Programmed Death 1 and Programmed Death-Ligand 1 Inhibitors in Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis of Trials. Chest 2017; 152: 271-281.

22. Falk AT, Yazbeck N, Guibert N et al. Effect of mutant variants of the KRAS gene on PD-L1 expression and on the immune microenvironment and association with clinical outcome in lung adenocarcinoma patients. Lung Cancer 2018; 121: 70-75.
23. Skoulidis F, Goldberg ME, Greenawalt DM et al. STK11/LKB1 Mutations and PD-1 Inhibitor Resistance in KRAS-Mutant Lung Adenocarcinoma. Cancer Discov 2018; 8: 822-835.
24. Soo RA, Lim SM, Syn NL et al. Immune checkpoint inhibitors in epidermal growth factor receptor mutant non-small cell lung cancer: Current controversies and future directions. Lung Cancer 2018; 115: 12-20.
25. Dong ZY, Zhang JT, Liu SY et al. EGFR mutation correlates with uninflamed phenotype and weak immunogenicity, causing impaired response to PD-1 blockade in non-small cell lung cancer. Oncoimmunology 2017; 6: e1356145.
26. Gainor JF, Shaw AT, Sequist LV et al. EGFR Mutations and ALK Rearrangements Are Associated with Low Response Rates to PD-1 Pathway Blockade in Non-Small Cell Lung Cancer: A Retrospective Analysis. Clin Cancer Res 2016; 22: 4585-4593.
27. Akbay EA, Koyama S, Carretero J et al. Activation of the PD-1 pathway contributes to immune escape in EGFR-driven lung tumors. Cancer Discov 2013; 3: 1355-1363.
28. Lee CK, Man J, Lord S et al. Checkpoint Inhibitors in Metastatic EGFR-Mutated Non-Small Cell Lung Cancer-A Meta-Analysis. J Thorac Oncol 2017; 12: 403-407.
29. Lisberg A, Cummings A, Goldman JW et al. A Phase II Study of Pembrolizumab in EGFR-Mutant, PD-L1+, Tyrosine Kinase Inhibitor Naive Patients With Advanced NSCLC. J Thorac Oncol 2018; 13: 1138-1145.
30. Welsh SJ, Rizos H, Scolyer RA, Long GV. Resistance to combination BRAF and MEK inhibition in metastatic melanoma: Where to next? Eur J Cancer 2016; 62: 76-85.
31. Wilmott JS, Long GV, Howle JR et al. Selective BRAF inhibitors induce marked T-cell infiltration into human metastatic melanoma. Clin Cancer Res 2012; 18: 1386-1394.
32. Dudnik E, Peled N, Nechushtan H et al. BRAF Mutant Lung Cancer: Programmed Death Ligand 1 Expression, Tumor Mutational Burden, Microsatellite Instability Status, and Response to Immune Check-Point Inhibitors. J Thorac Oncol 2018; 13: 1128-1137.
33. Noonan SA, Berry L, Lu X et al. Identifying the Appropriate FISH Criteria for Defining MET Copy Number-Driven Lung Adenocarcinoma through Oncogene Overlap Analysis. J Thorac Oncol 2016; 11: 1293-1304.
34. Sabari JK, Leonardi GC, Shu CA et al. PD-L1 expression, tumor mutational burden, and response to immunotherapy in patients with MET exon 14 altered lung cancers. Ann Oncol 2018; 29: 2085-2091.

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Tables

Table 1: Clinical and biological description according to mutation type

Table 2: PFS according to primary oncogenic driver from initiation of ICI

Figures Legend

Figure 1: Best response to ICI according to RECIST criteria (PD Progressive disease, SD Stable disease, PR Partial response, CR Complete Response).

Figure 2: Overall survival (on the left) and progression-free survival (on the right) in the whole cohort (upper figures) and in each subgroup (lower figures).

Figure 3: PFS according to oncogenic drivers' variants and PDL1 expression.

Online Supplementary data

S1: Consort Diagram

S2: Distribution of patients according to their molecular status.

S3: Treatments description.

S4: PDL1 expression according to mutation type.

S5: PDL1 level of expression for each molecular subgroup.

S6: Best response to ICI treatment (first line of immunotherapy) according to RECIST and oncogenic driver.

S7: Univariate analysis of OS from initiation of immunotherapy according to oncogenic driver variants.

S8: Univariate analysis of OS from initiation of immunotherapy according to clinical and biological characteristics.

S9: Univariate analysis of PFS from initiation of immunotherapy according to clinical and biological characteristics.

S10: Univariate analysis of PFS according to oncogenic driver variants from initiation of immunotherapy

S11: Rate of hyperprogression

S12: Overall survival and Progression free survival according to KRas type of mutation: Transition vs Transversion

S13: Univariate analysis of PFS according to PDL1 expressions, smoking habit, line of ICI introduction for each oncogenic driver subgroup.

S14: Overview of main results.

Article type: original article

Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry

J. Mazières[1], A. Drilon[2], A. Lusque[3], L. Mhanna[1], A.B. Cortot[4], L. Mezquita[5], A.A. Thai [6], C. Mascaux[7], S. Couraud[8], R. Veillon[9], M. Van Den Heuvel[10], J. Neal[11], N. Peled[12], M. Früh[13], T. L. Ng[14], V. Gounant[15], S. Popat[16], J. Diebold[17], J. Sabari[2], V.W. Zhu[18], S.I. Rothschild[19], P. Bironzo[20], A. Martinez[21], A. Curioni-Fontecedro[22], R. Rosell[23], M. Lattuca-Truc[24], M. Wiesweg[25], B. Besse[5], B. Solomon[6], F. Barlesi[7], R.D. Schouten [10], H. Wakelee[11], D.R. Camidge[14], G. Zalcman[15], S. Novello[20], S. I. Ou[18], J. Milia[1], O. Gautschi [17].

[1] Thoracic Oncology Department, Toulouse University Hospital, Université Paul Sabatier, Toulouse, France

[2] Early Drug Development service, Memorial Sloan Kettering Cancer Center, New York, United States.

[3] Biostatistics Unit, Institut Claudius Regaud, IUCT-O, Toulouse, France

[4] Thoracic Oncology Department, Lille Universitary hospital, Lille University, Lille, France.

[5] Medical oncology department, Institut d'Oncologie Thoracique, Institut Gustave Roussy, Villejuif, France.

[6] Medical Oncology department, Peter MacCallum Cancer Institute, Melbourne, Australia.

[7] Multidisciplinary Oncology and Therapeutic Innovations Department, Assistance Publique Hôpitaux de Marseille, Aix Marseille University, CNRS, INSERM, CRCM, Marseille, France.

[8] Respiratory diseases and thoracic oncology department, Lyon Sud Hospital, Cancer Institute of Hospices Civils de Lyon, Lyon 1 University, France.

[9] Pulmonology Department, Bordeaux University Hospital, Pessac, France.

[10] Faculty of medical science, Radboud university medical center, Nijmegen, the Netherlands.

[11] Division of Oncology, Department of Medicine. Stanford Cancer Institute/Stanford University. Stanford, CA, USA.
[12] Soroka Medical Center & Ben-Gurion University, Beer-Sheva, Israel.
[13] Department of Oncology, Haematology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland.
[14] Thoracic Oncology Department, University of Colorado Cancer Center, Aurora, Colorado, USA.
[15] Department of Thoracic Oncology, Paris-Nord, Bichat-Claude Bernard Hospital, APHP, Paris, France.
[16] Royal Marsden Hospital, London, United Kingdom.
[17] Pathology Department, University of Bern and Cantonal Hospital, Luzern, Switzerland.
[18] Department of Medicine, Division of Hematology-Oncology, University of California Irvine School of Medicine, Orange, CA, USA.
[19] Department Internal Medicine, University Hospital Basel, Medical Oncology, Basel, Switzerland.
[20] Department of Oncology, University of Torino, Torino, Italy.
[21] Medical Oncology Department, Vall d'Hebron Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain.
[22] Center of Hematology and Oncology University Hospital Zurich, Switzerland.
[23] Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Badalona, Spain; Germans Trias i Pujol Research Institute (IGTP), Badalona, Spain
[24] Pulmonology department, Grenoble universitary hospital, Grenoble, France.
[25] Department of Medical Oncology, West German Cancer Center, University Hospital Essen, University Duisburg-Essen, Germany.

CORRESPONDING AUTHOR
Prof Julien Mazières,
Thoracic Oncology Department
Hôpital LARREY
CHU Toulouse
24 Chemin de Pouvourville
31059 TOULOUSE

FRANCE
Tel: +33 567 771 837
Fax: +33 567 771 486
Email: mazieres.j@chu-toulouse.fr

Abstract:

Background: Anti-PD1/PD-L1 directed immune-checkpoint-inhibitors (ICI) are widely used to treat patients with advanced non-small cell lung cancer (NSCLC). The activity of ICI across NSCLC harboring oncogenic alterations is poorly characterized. The aim of our study was to address the efficacy of ICI in the context of oncogenic addiction.

Patients and methods: We conducted a retrospective study for patients receiving ICI monotherapy for advanced NSCLC with at least one oncogenic driver alteration. Anonymized data were evaluated for clinicopathologic characteristics and outcomes for ICI therapy: best response (RECIST 1.1), progression-free survival (PFS) and overall survival (OS) from ICI initiation. **The primary endpoint was** PFS **under ICI. Secondary endpoints were** best response (RECIST 1.1) and overall survival (OS) from ICI initiation.

Results: We studied 551 patients treated in 24 centers from 10 countries. The molecular alterations involved *KRAS* (n=271), *EGFR* (n=125), *BRAF* (n=43), *MET* (n=36), *HER2* (n=29), *ALK* (n=23), *RET* (n=16), *ROS1* (n=7), and multiple drivers (n=1). Median age was 60 years, gender-ratio was 1:1, never/former/current smokers were 28/51/21% respectively, and the majority of tumors were adenocarcinoma. The objective response rate by driver alteration was: *KRAS*=26%, *BRAF*=24%, *ROS1*=17%, *MET*=16%, *EGFR*=12%, *HER2*=7%, *RET*=6%, *ALK*=0%. In the entire cohort, median PFS was 2.8 months, OS 13.3 months and the best response rate 19%. In a subgroup analysis, median PFS (in months) was 2.1 for *EGFR*, 3.2 for *KRAS*, 2.5 for *ALK*, 3.1 for *BRAF*, 2.5 for *HER2*, 2.1 for *RET,* and 3.4 for *MET*. In certain subgroups, PFS was positively associated with PD-L1 expression (*KRAS*, *EGFR*) and with smoking status (*BRAF*, *HER2*).

Conclusions: ICI induced regression in some tumors with actionable driver alterations, but clinical activity was lower compared to the *KRAS* group and the lack of response in the ALK group was notable. Patients with actionable tumor alterations should receive targeted therapies and chemotherapy before considering immunotherapy.

Key words: Immunotherapy-lung cancer-oncogenic addiction

Key message:

Question: Is Immunotherapy efficient in patients with lung cancer and harboring an oncogenic addiction?

Findings: Patients' outcome treated with ICI monotherapy were consistent with ICI registration trials in the KRAS-subgroup but were inferior for patients with actionable driver mutations.

Meaning: ICI should thus only be considered after exhaustion of targeted and standard therapies.

Introduction

The management of patients with stage 4 non-small cell lung cancer (NSCLC) is currently undergoing significant transformation. Molecular testing, targeted therapies and immunotherapy are now part of routine clinical care [1]. Targeted therapies are efficient in the context of oncogenic driver mutations [2]. These treatments are usually associated with high response rate, but also with unavoidable development of resistance and tumor recurrence [3]. Therapeutic options are restrained in patients after exhaustion of targeted therapies and chemotherapy. Immune checkpoint inhibitors (ICI) which block the Programmed Death-1 (PD-1) /Programmed Death Ligand 1 (PD-L1) axis are a new standard of care not only in pretreated patients, but also in the first line setting [4-6]. ICI response rates in general are approximately 20% in unselected NSCLC, but overall survival benefit was well documented in registration trials [7-10].

Whether ICIs alone or even in combination with TKIs would offer comparable benefit in oncogene addicted subtypes of NSCLC as much as in the general unselected NSCLC population has been raised as a relevant question [11]. We may expect that immunotherapy may transform the important tumor responses achieved with targeted inhibitors in prolonged remissions. Nevertheless, data obtained from subgroups in clinical trials [9,10,12] and from investigators observations have shown rather weak activity of ICI in NSCLC patients harboring actionable driver mutations [13]. Many arguments have been proposed including low immunogenicity of tumors with single oncogenic addiction, inconstant PD-L1 expression, high proportion of never-smokers in this population, or low tumor mutational burden [11]. Therefore, the optimal use of ICI therapy in patients with actionable driver mutations remains an important field of ongoing research.

The purpose of this study was to analyze the clinical activity of ICI therapy in the context of oncogenic driver alterations. We previously conducted registry studies on targeted therapies for NSCLC with *ROS1*, *HER2*, *BRAF* and *RET* alterations [14-18]. We used our established network to perform a wide international cohort of patients with molecularly defined NSCLC. Hereinafter, we present the results for the whole cohort, and for individual molecular subgroups.

Patients and methods

Study objectives.

The primary objective of our study was to describe the progression-free survival (PFS) of patients treated with PD1/PD-L1 checkpoint inhibitors (ICI) in each subgroup carrying a molecular abnormality, namely *EGFR*, *ALK*, *ROS1*, *HER2*, *BRAF*, *MET*, *RET* and *KRAS*. The secondary objectives were both the best overall response (that was not confirmed by a second measurement) and the overall survival for each molecular subgroup. We also analyzed the outcome of patients according to smoking status, line of treatment, and PD-L1 expression.

Patients' selection

A global multicenter network of thoracic oncologists accrued patients in this registry. Investigators were identified via an ongoing collaboration established by our prior registries [14-18]. Eligible patients had 1) a pathological diagnosis of lung cancer according to IASLC/OMS classification; 2) local testing positive (either direct sequencing or NGS on validated platforms) for at least one oncogenic driver mutation: *EGFR* (exon 18-21) activating mutation, *HER2 (exon 20)* activating mutation, *KRAS* mutation, *BRAF* (exon 15) mutation, *MET* amplification or exon 14 mutation, *ALK* rearrangement, *ROS1* rearrangement or *RET* rearrangement; 3) single agent ICI therapy with commercial anti-PD1/PD-L1-antibodies ~~out from a clinical trial~~; 4) local response assessment according to RECIST1.1 criteria; 5) follow-up with survival status. Optionally, investigators were asked to record immunotherapy-related adverse events (irAE), and PD-L1 expression in tumor cells through local immunohistochemistry tests.

PD-L1 analysis

PD-L1 analysis was performed in each center according to local procedures. Antibodies used were E1L3N (32.8%), SP142 (31.7%), 22C3 (22.2%), SP263 (6.7%), 28-8 (5.6%), and others (1.1%). Results were provided in percentage of staining of tumor cells with 3 cut-off levels: 1%, 10% and 50%.

Ethical considerations

The study was approved by the national ethics committees of France (CEPRO 2017-043, CNIL Nh22181405l) and Switzerland (Swissethics/EKNZ ID 2017-01530). Participating centers were responsible for patients' consent and institutional approval. All contributors were trained in Good Clinical Practice. The study was a purely

academic collaboration granted by both Toulouse and Lucerne Hospitals and was not funded by industry.

Data collection and response assessment

Anonymized clinical data were recorded by local investigators using electronic case report forms (eCRF) in a password-protected secure online portal from the University of Toulouse [https://ec.claudiusregaud.fr/CSOnline/]. Data were centrally collected at the University of Toulouse (France). The registry was open for enrolment from May 2017 until April 2018. Best response to systemic therapies, defined as a complete or partial response achieved at least once during the course of therapy, was assessed locally using RECIST v1.1 criteria. Patients treated in clinical trials were not included in our study.

Statistical methods

All statistical evaluations were performed by the trial statistician (AL), according to the predefined plan as stated in the protocol. Data were summarized according to frequency and percentage for qualitative variables, and by median and range for quantitative variables. The 95% confidence interval for response rate was calculated using the exact binomial distribution. PFS was measured as the time from the first administration of ICI therapy to progression defined by RECIST1.1, or death due to any cause. Patients alive without progression at the time of analysis were censored at the initiation of a new therapy or last follow-up. Overall survival was measured as the time from the first administration of ICI therapy to death due to any cause. Patients alive at the time of analysis were censored at the last follow-up. Survival data were estimated using the Kaplan–Meier method and compared using the log-rank test in overall cohort and oncogenic driver subgroups. Statistical analyses were carried out using STATA 13.1 software (StataCorp, TX, USA).

Results

Patients' characteristics

During an enrolment phase of almost one year, the registry included 551 patients from 24 centers in 10 countries. The molecular alterations involved *KRAS* (n=271), *EGFR* (n=125), *BRAF* (n= 43, *V600E* n=17, other n=18), *MET* (n=36, *MET* amplification n=13, exon 14 skipping mutation n=23), *HER2* (n=29), *ALK* (n=23), *RET* (n=16), *ROS1* (n=7).

34 patients with more than one driver were allocated to the dominant oncogenic driver. Details are provided in the supplementary data (S1:CONSORT diagram and S2). Median age was 60 years (range: 29-83). Gender-ratio was 1:1. Smoking status was 28% never-smokers, 51% former smokers, and 21% current smokers. The majority (96%) of tumors were adenocarcinoma. At the time of immunotherapy initiation, most patients had ECOG Performance Status (PS) of 1 (64%), while fewer patients were PS0 (21%), PS2 (11%), and PS3/4 (4%). All patients presented an advanced tumor stage at the beginning of immunotherapy. The clinical characteristics of each subgroup are reported in Table 1.

Treatment characteristics and safety

Most (94%) patients received anti-PD1-antibodies (nivolumab n = 466, pembrolizumab n = 48, other n = 6), fewer patients (6%) had anti-PD-L1-antibodies (atezolizumab n = 19, durvalumab n = 11, other n = 1). ICIs were given in the first (5%), second (41%), third (26%), fourth line (13%) or in later lines (14%) of treatment (S3). The recording of significant (grade 3-4) immunotherapy-related adverse events (irAE) was optional. From 462 patients with available data, 50 (10.8%) had grade 3-5 irAEs, including 36 (7.8%) of grade 3, 13 (2.8%) of grade 4 and 1 of grade 5 (0.2%, endocrine disorder). The pneumonitis rate was in the expected range (13 cases, 2.8% including 8 grade 3 and 5 grade 4). No unexpected irAEs were recorded.

PD-L1 expression

PD-L1 status determined by immunohistochemistry was available for 214 patients. The median number of positive cells was 10%. Using a 1% cut-off, one third were negative (33.2%) and two-third positive (66.8%). Using a 10% cut-off, half of the tumors was negative (49.7%) and half positive (50.3%). Using a 50% cut-off, one-third of the tumors was positive (33.9%). Looking into each subgroup, we found that median percentage of cells expressing PD-L1 was 0 in *HER2* (n= 13), 3.5 in *EGFR* (n=38), 7.5 in *ALK* (n=10), 12.5 in *KRAS* (n=80), 26 in *RET* (n=6), 30 in *MET* (n=15), 50 in *BRAF* (n=9) and 90 in *ROS1* (n=5) subgroups. S4 and S5.

Clinical outcomes

Response rate

Responses were not confirmed by a second measurement. The rate of any partial or complete response was 19% [95%CI: 16-23%], ranging from 0% in ALK patients to 26% in KRAS mutated patients. If we consider the KRAS patients as a control group and exclude them from the analysis, the best response rate for patients harboring all other molecular alterations was 12.7%. We then classified the subgroups according to the rate of progressive disease. Progressive disease (PD) was observed in 46% for *BRAF*, 50% for *MET*, 51% for *KRAS*, 67% for *HER2*, 67% for *EGFR*, 68% for *ALK*, 75% for *RET* and 83% for *ROS1*. Fig. 1, S6.

Overall survival

In the entire cohort, median follow-up was 16.1 months, and median OS from start of ICI therapy was 13.3 months [10.0-14.9] (Fig. 2). Median OS (in months) for individual molecular subgroups was 10.0 [6.7;14.2] for *EGFR* mutated patients, 13.5 [9.4;15.6] for *KRAS*, 17.0 [3.6;NR] for *ALK*, 13.6 [7.4;22.5] for *BRAF*, 20.3 [7.8;NR] for *HER2*, 21.3 [3.8;28.0] for *RET* and 18.4 [7.0;NR] for *METS7*. In the univariate analysis, OS did not correlate with gender, age, smoking, number of prior therapies, or PD-L1 expression (S8).

Progression-free survival

In the entire cohort, median PFS was 2.8 months [95%IC 2.5-3.1]. Median PFS (in months) for individual molecular subgroups was 2.1 [1.8;2.7] for *EGFR*, 3.2 [2.7;4.5] for *KRAS*, 2.5 [1.5;3.7] for *ALK*, 3.1 [1.8;4.6] for *BRAF*, 2.5 [1.8;3.5] for *HER2*, 2.1 [1.3;4.7] for *RET* and 3.4 [1.7;6.2] for *MET* (Fig. 2). Long-term responders were more frequent in *KRAS* (12-months PFS: 25.6 %), *MET* (23.4%) and *BRAF* (18.0%) subgroups, than in *EGFR* (6.4%), *ALK* (5.9%), *HER2* (13.6%) and *RET* (7.0%) subgroups (Table 2). If we exclude KRAS patients from the analysis (n=279 patients with all other alterations), median PFS was 2.4 months.

In the univariate analysis, PFS significantly correlated with smoking (median PFS: 2.5, 2.8 and 3.5 months for never smokers, former smokers and current smokers, respectively, $p < 0.0001$), and with PD-L1 expression (3.0 *vs* 4.2 months for negative and positive expression of PD-L1, $p = 0.02$). However, PFS did not correlate with gender ($p = 0.5$), age ($p = 0.3$) or number of previous lines of treatment ($p = 0.08$). (S9 and S10). Interestingly, a higher rate of rapid progression (within 2 months) was observed for EGFR (44.8%), ALK (45.5%), ROS1 (42.9%) and RET (43.8%) patients than for KRAS (36%) (S11) respectively.

Molecular subgroup analyses

KRAS mutations were identified in 271 patients. PFS was not significantly different regarding *KRAS* mutation subtype if we compare *G12C* (n = 100) to other mutations (n = 143, *p* = 0.47) or *G12D* (n = 39) *vs* other *KRAS* mutations (n = 204, *p* = 0.40). PFS did also not correlate with smoking (*p* = 0.98), or with the number of previous lines of treatment. In patients with available PD-L1 expression data (n = 95), PD-L1 positive expression was significantly (*p* = 0.01) correlated with a longer PFS (median PFS: 7.2 vs 3.9 months) (Fig 3). We also separate patients harbouring KRAS transition (G12D, G13D, G12S) from KRAS transversion (G12C, G12A, G12V, G13C). PFS was not impacted by the nature of KRas alteration (2.9 months for transition, 4.0 for transversion, p = 0.27, (S12).

EGFR mutations were reported in 125 patients. PFS was significantly different across molecular subgroups ranging from 1.4 month in *T790M* and complex mutations subgroup to 1.8 for exon 19, 2.5 for exon 21 and 2.8 for other mutations (*p* < 0.001). PFS correlated neither with smoking (*p* = 0.06), nor with the number of previous lines of treatment. PD-L1 positivity was significantly correlated with a longer PFS (2.8 months *vs.* 1.7, p=0.01) (Fig 3).

BRAF mutations were identified in 43 patients. PFS was significantly higher in smokers *vs.* never smokers (4.1 *vs.* 1.9 months, *p* = 0.03). Median PFS was numerically shorter in the V600E subgroup (1.8 months) compared to other *BRAF* mutations (4.1 months) but this difference did not reach significance (*p* = 0.20).

MET molecular alterations were found in 36 patients. Median PFS correlated neither with alteration subtype (exon 14 skipping mutation *vs* other MET alterations including MET amplification, *p* = 0.09), nor with smoking.

HER2 mutations were identified in 29 patients. PFS correlated with smoking (3.4 months for smokers *vs* 2.0 months for never smokers, *p* = 0.04).

Due to a low number of patients, *ALK*, *ROS1* and *RET* were analyzed together in a subgroup termed “rearrangements”. Median PFS was only slightly higher in never-smokers (2.6 months) than in smokers (1.8 months, *p* = 0.03). PD-L1 was not available in enough patients but no tumor response was reported in patients from this group in the context of PD-L1 positivity. (S13, S5). Main results for all cohorts are presented in S14.

Discussion

The standard of care for patients with actionable driver alterations (*EGFR*, *ALK*, *ROS1* and *BRAF-V600E*) is a targeted therapy. A targeted therapy should also be considered for *HER2 [16]*, *RET [17],* and *MET* alterations. After exhaustion of targeted agents and chemotherapy, immunotherapy may be considered as a salvage treatment. Nevertheless, evidence to support the role of ICI in this setting is controversial, as *EGFR* and *ALK* alterations have been associated with low ICI efficacy in prior studies [19]. To address this issue, we conducted a global "real world" study. Our study was retrospective and had other limitations, including reporting bias, lack of central molecular and radiologic assessment, and variable scanning intervals. Nevertheless, we obtained new findings of clinical relevance.

In the overall cohort, the best response with ICI therapy by RECIST was 19%, and median PFS was 2.8 months. This result was mainly driven by the large KRAS subgroup, and it is in concordance with registration trials testing immunotherapy in pretreated patients, regardless *EGFR* or *ALK* status [9] [10]. Regarding molecular subgroups, we confirmed that patients with *KRAS*-mutant NSCLC derived a greater benefit from ICI than *EGFR*-mutant NSCLC, as reported in the previous Checkmate-057 trial [9]. It has been reported that *KRAS*-mutant NSCLC are more likely to express PD-1 and PD-L1[20]. Calles *et al.* also showed that *KRAS* mutant tumors were more likely to express PD-L1 when the patient was a smoker [21]. In a recent study, Falk *et al.* found that *KRAS*-mutant tumor cells significantly express more PD-L1 than KRAS-WT cells. Interestingly, the distribution of PD-L1 expression in tumor cells was significantly related to the subtype of mutant *KRAS*, with tumors expressing the *G12V* substitution harboring a higher expression of PD-L1 [22]. In our study, we have not been able to detect a significant correlation between KRAS mutation subtypes and PFS, but we confirmed that PD-L1 expression is associated with a better outcome. Recently, *STK11/LKB1* co-mutation in KRAS-mutant NSCLC was reported as a new predictive marker for tumor resistance to ICI therapy [23]. *STK11* was not part of routine testing and our study did not include tissue collection, therefore, future studies will have to validate this interesting finding in a larger cohort. ICI are thus an adequate treatment for *KRAS* mutated patients and markers including PD-L1 may identify the best candidates in a better way. Nevertheless, the limited number of patients with available PDL1 status and the heterogeneity of the tests did not allow us to draw a definitive conclusion on its potential interest.

Interestingly, if we exclude KRAS patients from our analysis and focus only on targetable drivers, the outcome is lower with 12.7% response rate and 2.4 months PFS. Recent studies showed an inverse relationship between PD-L1 expression and EGFR mutations and no association between PD-L1 expression and ALK rearrangement was reported. Moreover, an uninflamed tumor microenvironment is often reported in the context of oncogenic addiction [24,25]. Gainor *et al.* also suggested that a dearth of tumor-infiltrating $CD8^+$ lymphocytes, may explain the low response rate to PD-1 axis inhibitors observed amongst EGFR- and ALK-driven NSCLC [26].

Concerning patients with *EGFR* mutation, the role of ICI therapy is still controversial. Murine models have shown that PD-L1 can be overexpressed in the context of *EGFR* mutation, and significant response has been reported to anti-PD1-antibodies in preclinical studies [27]. In a retrospective study, Gainor *et al.* identified a very low response rate in patients with *EGFR*-mutant NSCLC treated with ICI-therapy (1 of 28, 3.6%) [13]. A recent meta-analysis including 3 randomized trials of immunotherapy in TKI-pretreated patients reported that ICI do not improve OS compared to docetaxel in patients *with EGFR*-mutant NSCLC [28]. In addition, a recent phase II trial of pembrolizumab in TKI-naive patients with PD-L1 positive *EGFR*-mutant NSCLC showed no RECIST responses in the first 11 patients and the trial was stopped [29]. In the phase II trial ATLANTIC of durvalumab in EGFR/ALK mutant NSCLC, response rate was 3.6% for PD-L1 < 25%, and 12.2% for PD-L1 > 25%. Median PFS was 1.9 month [19]. We found similar outcomes in our cohort, with a 12% RR and 2.1 months PFS. Together, these results support the use of PD-L1 for decision making regarding ICI therapy in TKI-pretreated patients with EGFR-mutant NSCLC, although even with higher levels of expression, response rates remain low compared to targeted therapy [29]. Benefit has, however, been reported in patients with EGFR mutations with the combination of carboplatin, paclitaxel, bevacizumab and atezolizumab in the IMpower150 trial [5].

BRAF mutations were associated with slightly better outcomes compared to *EGFR* mutations (RR 24% and PFS 3.1 months). The potential efficacy of immunotherapy in *BRAF* mutant melanoma has already been suggested [30]. It has been shown in melanoma that BRAF inhibition has favorable effects in the tumor microenvironment [31]. Recently, Dudnik et al. reported frequent expression of PDL1 and comparable

PFS (3.7 months) in BRAF V600E mutated patients [32]. In our study, PFS in patients with *BRAF*-mutant NSCLC was positively associated with smoking status. It thus appears that immunotherapy may be considered in *BRAF* positive patients after targeted therapy and one line of chemotherapy.

Our MET altered cohort contained several different potential subgroups, while MET exon 14 skip mutations may be most clearly defined, the other category, which included both MET amplification at various levels may or may not represent true oncogene-addicted states [33]. ICI activity in MET exon 14 has recently been reported to be very low even in the setting of high TMB or high PD-L1 [34]. Of note, amongst the 5 responses seen to ICI in the MET cohort these occurred only in 2 patients with exon 14 skipping mutations.

ALK, *ROS1* and *RET* translocation represent a small subgroup of NSCLC. Nevertheless, several cases were included in our study. PD-L1 expression was relatively high in those cases. However, most tumors were refractory to ICI therapy. These observations were consistent with other studies, namely with ATLANTIC for ALK, and with a cohort study from MSKCC for RET [34]. Moreover, only one ROS1 patients responded, the remaining 6 patients progressed through first CT-scan. Although these data are preliminary, we do not recommend ICI as single agents in patients with ALK/ROS1/RET rearranged NSCLC. Further studies are requested to see if patients may do better with combination therapies, as suggested for EGFR [5].

In conclusion, patients' outcome treated with ICI monotherapy overall were consistent with ICI registration trials, based on the large KRAS-subgroup in our study. However, outcomes for patients with actionable driver mutations (EGFR, ALK, ROS1) were inferior and ICI should only be considered after exhaustion of targeted therapies and in some cases, potentially in all other therapies including standard and salvage chemotherapies. Indeed in the case of ALK+ disease, our data, now added to several others, demonstrate that not a single ALK+ NSCLC case has had a documented response to monotherapy from ICI [13,19] . We think that there are two ways to optimize the use of immunotherapy in the context of oncogenic addiction. The first one is to combine immunotherapy with other drugs such as chemotherapy and anti-angiogenic agents. The second one is to identify new relevant biomarkers besides PD-L1 expression and TMB considering the complex molecular biology of NSCLC.

NOTE

Preliminary results were presented at the ASCO-SITC meeting (2018 January 26th, San Francisco, abstract #172) and at the ASCO Annual Meeting, (2018 June 1st, abstract #9010, oral communication in Clinical Science Symposium).

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BIBLIOGRAPHY

1. Doroshow DB, Herbst RS. Treatment of Advanced Non-Small Cell Lung Cancer in 2018. JAMA Oncol 2018; 4: 569-570.
2. Resources NGC. NCCN Framework for Resource Stratification of NCCN Guidelines (NCCN Framework™). In NCCN Guidelines® & Clinical Resources. https://www.nccn.org/framework/ 2019.
3. Cortot AB, Janne PA. Molecular mechanisms of resistance in epidermal growth factor receptor-mutant lung adenocarcinomas. Eur Respir Rev 2014; 23: 356-366.
4. Reck M, Rodriguez-Abreu D, Robinson AG et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016; 375: 1823-1833.
5. Socinski MA, Jotte RM, Cappuzzo F et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N Engl J Med 2018; 378: 2288-2301.
6. Gandhi L, Rodriguez-Abreu D, Gadgeel S et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med 2018; 378: 2078-2092.
7. Brahmer J, Reckamp KL, Baas P et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. New England Journal of Medicine 2015; 373: 123-135.
8. Borghaei H, Brahmer J. Nivolumab in Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 2016; 374: 493-494.
9. Borghaei H, Paz-Ares L, Horn L et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. New England Journal of Medicine 2015; 373: 1627-1639.
10. Herbst RS, Baas P, Kim DW 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: 1540-1550.
11. Gettinger S, Politi K. PD-1 Axis Inhibitors in EGFR- and ALK-Driven Lung Cancer: Lost Cause? Clin Cancer Res 2016; 22: 4539-4541.
12. Fehrenbacher L, Spira A, Ballinger M 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: 1837-1846.
13. Naidoo J, Schindler K, Querfeld C et al. Autoimmune Bullous Skin Disorders with Immune Checkpoint Inhibitors Targeting PD-1 and PD-L1. Cancer Immunol Res 2016; 4: 383-389.
14. Gautschi O, Bluthgen MV, Smit E et al. Targeted therapy for BRAF-mutant lung cancer: Results from the European EURAF cohort study In ELCC. Geneva: 2015.
15. Mazieres J, Zalcman G, Crino L et al. Crizotinib therapy for advanced lung adenocarcinoma and a ROS1 rearrangement: results from the EUROS1 cohort. Journal of Clinical Oncology 2015; 33: 992-999.
16. Mazieres J, Barlesi F, Filleron T et al. Lung cancer patients with HER2 mutations treated with chemotherapy and HER2-targeted drugs: results from the European EUHER2 cohort. Annals of Oncology 2015.
17. Gautschi O, Milia J, Filleron T et al. Targeting RET in Patients With RET-Rearranged Lung Cancers: Results From the Global, Multicenter RET Registry. J Clin Oncol 2017; 35: 1403-1410.
18. Mazieres J, Peters S, Lepage B et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. J Clin Oncol 2013; 31: 1997-2003.
19. Garassino MC, Cho BC, Kim JH et al. Durvalumab as third-line or later treatment for advanced non-small-cell lung cancer (ATLANTIC): an open-label, single-arm, phase 2 study. Lancet Oncol 2018; 19: 521-536.
20. Chen N, Fang W, Lin Z et al. KRAS mutation-induced upregulation of PD-L1 mediates immune escape in human lung adenocarcinoma. Cancer Immunol Immunother 2017; 66: 1175-1187.
21. Khunger M, Rakshit S, Pasupuleti V et al. Incidence of Pneumonitis With Use of Programmed Death 1 and Programmed Death-Ligand 1 Inhibitors in Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis of Trials. Chest 2017; 152: 271-281.

22. Falk AT, Yazbeck N, Guibert N et al. Effect of mutant variants of the KRAS gene on PD-L1 expression and on the immune microenvironment and association with clinical outcome in lung adenocarcinoma patients. Lung Cancer 2018; 121: 70-75.
23. Skoulidis F, Goldberg ME, Greenawalt DM et al. STK11/LKB1 Mutations and PD-1 Inhibitor Resistance in KRAS-Mutant Lung Adenocarcinoma. Cancer Discov 2018; 8: 822-835.
24. Soo RA, Lim SM, Syn NL et al. Immune checkpoint inhibitors in epidermal growth factor receptor mutant non-small cell lung cancer: Current controversies and future directions. Lung Cancer 2018; 115: 12-20.
25. Dong ZY, Zhang JT, Liu SY et al. EGFR mutation correlates with uninflamed phenotype and weak immunogenicity, causing impaired response to PD-1 blockade in non-small cell lung cancer. Oncoimmunology 2017; 6: e1356145.
26. Gainor JF, Shaw AT, Sequist LV et al. EGFR Mutations and ALK Rearrangements Are Associated with Low Response Rates to PD-1 Pathway Blockade in Non-Small Cell Lung Cancer: A Retrospective Analysis. Clin Cancer Res 2016; 22: 4585-4593.
27. Akbay EA, Koyama S, Carretero J et al. Activation of the PD-1 pathway contributes to immune escape in EGFR-driven lung tumors. Cancer Discov 2013; 3: 1355-1363.
28. Lee CK, Man J, Lord S et al. Checkpoint Inhibitors in Metastatic EGFR-Mutated Non-Small Cell Lung Cancer-A Meta-Analysis. J Thorac Oncol 2017; 12: 403-407.
29. Lisberg A, Cummings A, Goldman JW et al. A Phase II Study of Pembrolizumab in EGFR-Mutant, PD-L1+, Tyrosine Kinase Inhibitor Naive Patients With Advanced NSCLC. J Thorac Oncol 2018; 13: 1138-1145.
30. Welsh SJ, Rizos H, Scolyer RA, Long GV. Resistance to combination BRAF and MEK inhibition in metastatic melanoma: Where to next? Eur J Cancer 2016; 62: 76-85.
31. Wilmott JS, Long GV, Howle JR et al. Selective BRAF inhibitors induce marked T-cell infiltration into human metastatic melanoma. Clin Cancer Res 2012; 18: 1386-1394.
32. Dudnik E, Peled N, Nechushtan H et al. BRAF Mutant Lung Cancer: Programmed Death Ligand 1 Expression, Tumor Mutational Burden, Microsatellite Instability Status, and Response to Immune Check-Point Inhibitors. J Thorac Oncol 2018; 13: 1128-1137.
33. Noonan SA, Berry L, Lu X et al. Identifying the Appropriate FISH Criteria for Defining MET Copy Number-Driven Lung Adenocarcinoma through Oncogene Overlap Analysis. J Thorac Oncol 2016; 11: 1293-1304.
34. Sabari JK, Leonardi GC, Shu CA et al. PD-L1 expression, tumor mutational burden, and response to immunotherapy in patients with MET exon 14 altered lung cancers. Ann Oncol 2018; 29: 2085-2091.

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Tables

Table 1: Clinical and biological description according to mutation type

Table 2: PFS according to primary oncogenic driver from initiation of ICI

Figures Legend

Figure 1: Best response to ICI according to RECIST criteria (PD Progressive disease, SD Stable disease, PR Partial response, CR Complete Response).

Figure 2: Overall survival (on the left) and progression-free survival (on the right) in the whole cohort (upper figures) and in each subgroup (lower figures).

Figure 3: PFS according to oncogenic drivers' variants and PDL1 expression.

Online Supplementary data

S1: Consort Diagram

S2: Distribution of patients according to their molecular status.

S3: Treatments description.

S4: PDL1 expression according to mutation type.

S5: PDL1 level of expression for each molecular subgroup.

S6: Best response to ICI treatment (first line of immunotherapy) according to RECIST and oncogenic driver.

S7: Univariate analysis of OS from initiation of immunotherapy according to oncogenic driver variants.

S8: Univariate analysis of OS from initiation of immunotherapy according to clinical and biological characteristics.

S9: Univariate analysis of PFS from initiation of immunotherapy according to clinical and biological characteristics.

S10: Univariate analysis of PFS according to oncogenic driver variants from initiation of immunotherapy

S11: Rate of hyperprogression

S12: Overall survival and Progression free survival according to KRas type of mutation: Transition vs Transversion

S13: Univariate analysis of PFS according to PDL1 expressions, smoking habit, line of ICI introduction for each oncogenic driver subgroup.

S14: Overview of main results.

Table 1: Clinical and biological description according to mutation type

	EGFR N=125		KRAS N=271		ALK N=23		BRAF N=43		ROS1 N=7		HER2 N=29		RET N=16		MET N=36	
Gender (n=551)																
Male	48	38.4%	141	52%	12	52.2%	24	55.8%	5	71.4%	15	51.7%	7	43.8%	21	58.3%
Female	77	61.6%	130	48%	11	47.8%	19	44.2%	2	28.6%	14	48.3%	9	56.3%	15	41.7%
Smoking (n=551)																
Never Smoker	78	63.4%	12	4.6%	10	47.6%	11	26.2%	5	71.4%	14	51.9%	10	66.7%	8	23.5%
Former Smoker	38	30.9%	168	64.6%	8	38.1%	22	52.4%	2	28.6%	12	44.4%	4	26.7%	15	44.1%
Current Smoker	7	5.7%	80	30.8%	3	14.3%	9	21.4%	0	0%	1	3.7%	1	6.7%	11	32.4%
missing	2		11		2		1				2		1		2	
Histological Type (n=551)																
Adenocarcinoma	121	96.8%	262	96.7%	21	91.3%	40	93%	6	85.7%	28	96.6%	14	87.5%	34	94.4%
Squamous	1	0.8%	0	0%	0	0%	1	2.3%	0	0%	0	0%	0	0%	0	0%
Sarcomatoid	0	0%	1	0.4%	0	0%	0	0%	0	0%	0	0%	0	0%	1	2.8%
Large cell carcinoma	0	0%	6	2.2%	1	4.3%	1	2.3%	0	0%	1	3.4%	1	6.3%	0	0%
Not specified/other/missing	3	2.4%	2	0.7%	1	4.3%	1	2.3%	1	14.3%	0	0%	1	6.3%	1	2.8%
Age at Diagnosis (n=551)																
Median (year)	60		59		55		61		45		62		54.5		63	
Range (year)	33-80		30-83		30-73		42-75		42-67		31-77		29-73		40:82	

Table 2: PFS according to primary oncogenic driver from initiation of ICI

	EVT/N	Median PFS [95%CI] (months)	6-months PFS [95%CI]	12-months PFS [95%CI]
KRAS	208/271	3.2 [2.7; 4.5]	37.9 [32.1; 49.8]	25.6 [20.2; 31.3]
EGFR	117/125	2.1 [1.8; 2.7]	18.4 [12.1; 25.6]	6.4 [2.7; 12.1]
BRAF	34/43	3.1 [1.8; 4.6]	32.1 [18.3; 46.6]	18.0 [7.2; 32.7]
HER2	23/29	2.5 [1.8;3.5]	22.7 [8.9; 40.2]	13.6 [3.6; 30.1]
MET	26/36	3.4 [1.7; 6.2]	36.5 [20.7; 52.4]	23.4 [10.6; 39.0]
ALK	21/23	2.5 [1.5; 3.7]	11.8 [2.2; 30.2]	5.9 [0.4; 23.0]
ROS1	-	-	-	-
RET	15/16	2.1 [1.3; 4.7]	14.1 [2.3; 35.9]	7.0 [0.4; 27.1]

EVT Event; N Number

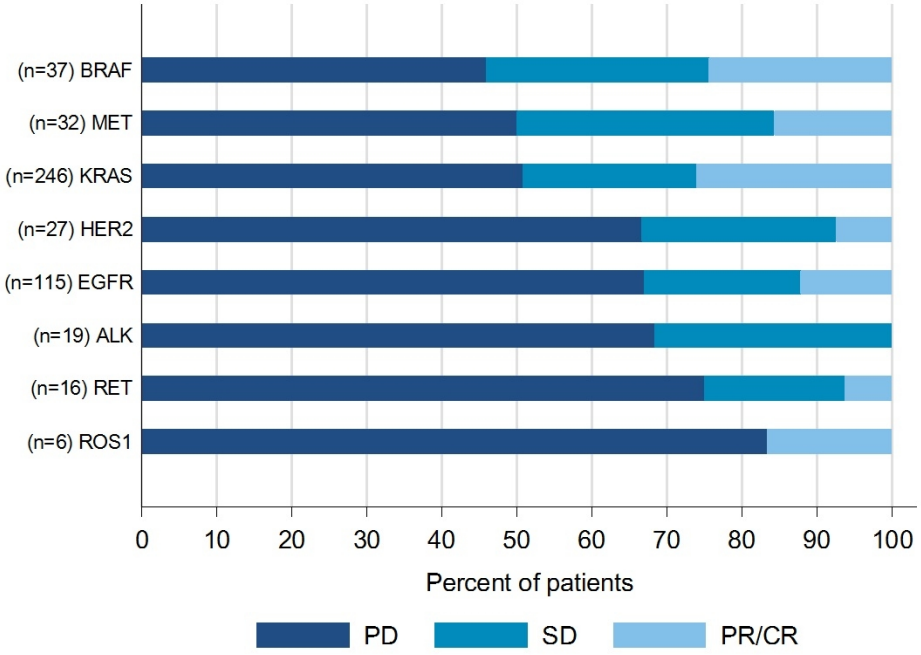


Figure 1: Best response to ICI according to RECIST criteria (PD Progressive disease, SD Stable disease, PR Partial response, CR Complete Response).

194x141mm (150 x 150 DPI)

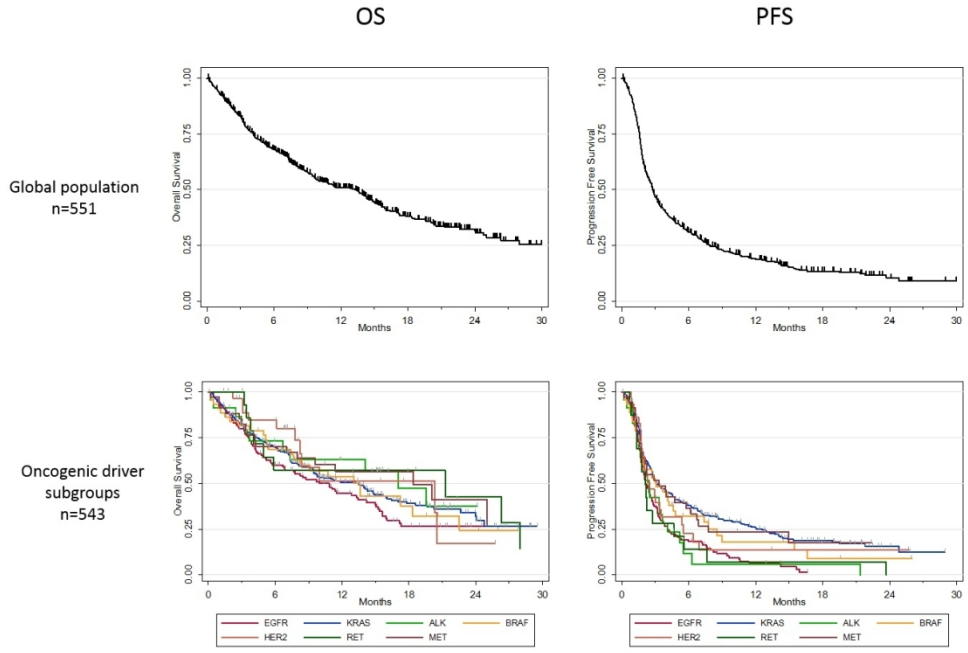


Figure 2: Overall survival (on the left) and progression-free survival (on the right) in the whole cohort (upper figures) and in each subgroup (lower figures).

236x158mm (150 x 150 DPI)

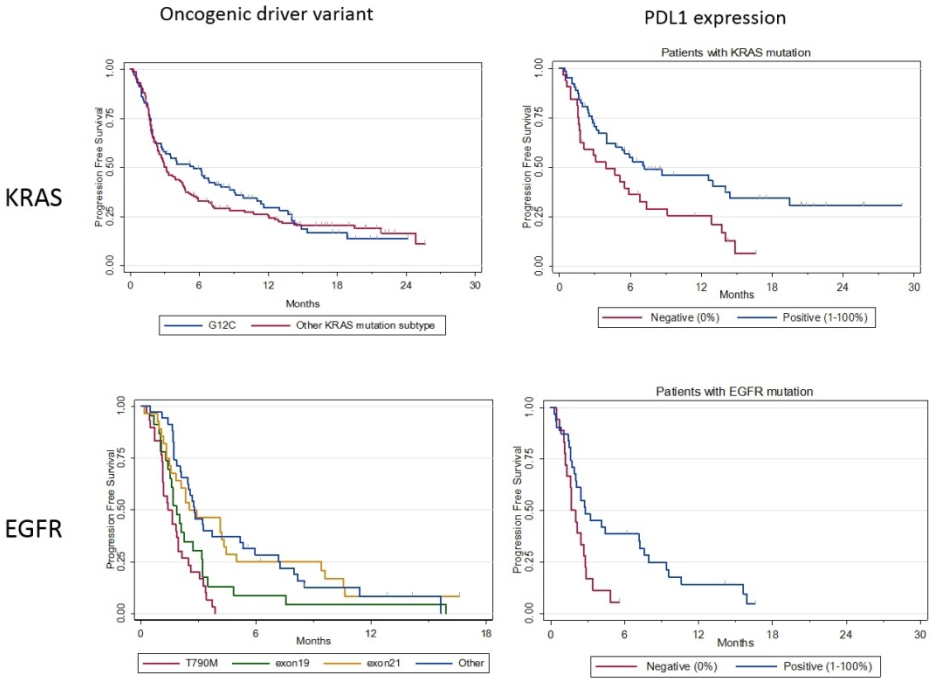
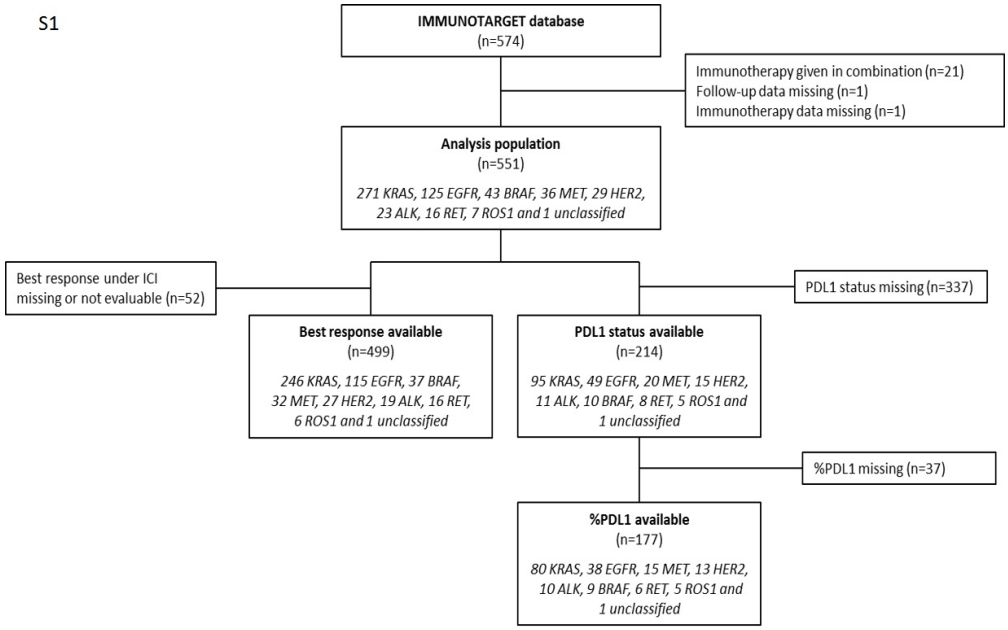


Figure 3: PFS according to oncogenic drivers' variants and PDL1 expression.

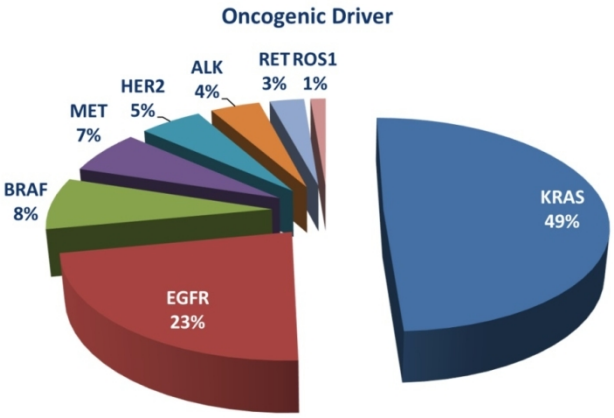
229x161mm (150 x 150 DPI)

S1



207x130mm (150 x 150 DPI)

S2



	N	%
KRAS	271	49
G12A	30	12.3
G12C	100	41.2
G12D	39	16
G12V	36	14.8
G12S	8	3.3
Other	30	12.3
Missing	28	
EGFR	125	23
Exon 18	4	3.4
Exon19	23	19.8
T790M	7	6
Exon21	28	24.1
Multiple with T790M	23	19.8
Other multiple mutations or rare mutations	31	26.7
Missing	9	
BRAF	43	8
V600E	17	48.6
Non V600E	18	51.4
Missing	8	
MET	36	7
Amplification	13	38.2
Exon14 mutation	23	69.7
HER2	29	5
ALK	23	4
Translocation	20	87
Mutation	1	4.3
Both	2	8.7
RET	16	3
KIF5B	6	75
Other	2	25
Missing	8	
ROS1	7	1

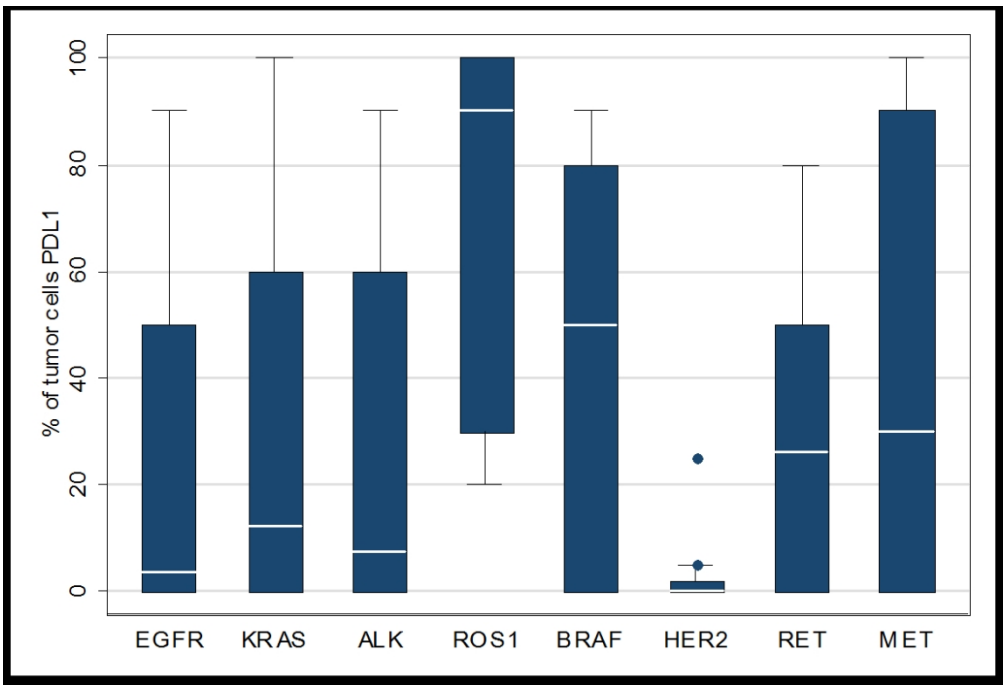
249x141mm (150 x 150 DPI)

S3:

		N	%
Anti PD1 n=520			
	Nivolumab	466	89.6
	Pembrolizumab	48	9.2
	Other	6	1.2
Anti PDL1 n=31			
	Atezolizumab	19	59.4
	Durvalumab	11	34.4
	Other	1	3.1
Line Immunotherapy n=551			
	1st line	30	5.4
	2nd line	227	41.2
	3rd line	144	26.1
	4th line	73	13.2
	>4th Line	77	14
Duration of the line (months) n=485			
		2.1	
	Median	0.03-27.4	
	Range	66	
	missing		
Number of injections n=470			
	Median	5	
	Range	1-68	
	Missing	81	

S4:

	EGFR N=125		KRAS N=271		ALK N=23		BRAF N=43		ROS1 N=7		HER2 N=29		RET N=16		MET N=36	
PDL1 Status available	N = 49		N = 95		N = 11		N = 10		N = 5		N = 15		N = 8		N = 20	
PDL1 Status																
Negative	18	36.7%	32	33.7%	4	36.4%	3	30%	0	0%	7	46.7%	2	25%	5	25%
Positive (>1%)	31	63.3%	63	66.3%	7	63.6%	7	70%	5	100%	8	53.3%	6	75%	15	75%
% of tumor cells																
PDL1 staining <10%	21	55.3%	39	48.8%	5	50%	3	33.3%	0	0%	11	84.6%	3	50%	6	40%
≥10%	17	44.7%	41	51.3%	5	50%	6	66.7%	5	100%	2	15.4%	3	50%	9	60%
missing	11		15		1		1		0		2		2		5	
% of tumor cells																
PDL1 staining <50%	27	71.1%	54	67.5%	6	60%	4	44.4%	2	40%	13	100%	3	50%	8	53.3%
≥50%	11	28.9%	26	32.5%	4	40%	5	55.6%	3	60%	0	0%	3	50%	7	46.7%
missing	11		15		1		1		0		2		2		5	
% of tumor cells PDL1 positive																
Median	3.5		12.5		7.5		50		90		0		26		30	
Range	0-90		0-100		0-90		0-90		20-100		0-25		0-80		0:100	
missing	11		15		1		1		0		2		2		5	



198x134mm (150 x 150 DPI)

S6:

	Treatment Best response						
	CR/PR*		SD		PD		
	N	%	N	%	N	%	Missing
Total	97	19.4	119	23.8	283	56.7	52
KRAS	64	26	57	23.2	125	50.8	25
EGFR	14	12.2	24	20.9	77	67	10
BRAF	9	24.3	11	29.7	17	45.9	6
HER2	2	7.4	7	25.9	18	66.7	2
MET	5	15.6	11	34.4	16	50	4
ALK	0	0	6	31.6	13	68.4	4
ROS	1	16.7	0	0	5	83.3	1
RET	1	6.3	3	18.8	12	75	0

*Complete Response CR, Partial Response PR, Stable disease (SD), Progressive Disease (SD)

S7:

	EVT/N	Median OS [95%CI] (Months)	p
KRAS			
G12C	51/100	15.6 [11.0; 19.6]	0.69
Other	78/143	10.0 [7.5; 14.8]	
EGFR			
T790 single or multiple	21/30	5.6 [2.8; 15.9]	0.03
Exon19	19/23	4.9 [3.2; 10.8]	
Exon21	19/28	10.9 [3.9; 15.4]	
other	16/35	12.8 [8.5; NR]	
BRAF			
V600E	11/17	8.2 [1.1; NR]	0.28
Other	9/18	17.2 [2.7; NR]	
MET			
Exon14 yes	9/23	25.0 [18.4; NR]	0.00
Exon14 no	7/10	8.0 [1.0; 11.4]	

EVT Event; N Number; NR Not Reached

S8:

	EVT/ N	Median OS [95%CI] (Months)	p
Gender :			
Male	139 / 274	13.6 [9.4; 16.4]	p = 0.92
Female	161 / 277	11.4 [9.6; 15.4]	
Age at diagnosis			
<= 60 years	157 / 284	11.3 [9.4; 14.9]	p = 0.73
> 60 years	143 / 267	13.6 [10.0; 17.0]	
Smoking :			
Never smoker	89 / 148	10.9 [8.2; 15.0]	p = 0.69
Former smoker	145 / 269	13.6 [10.0; 17.0]	
Current smoker	60 / 113	11.0 [8.0; 16.4]	
Stage at diagnosis			
IA-IIIA	48 / 99	15.2 [11.1; 24.0]	p = 0.11
IIIB-IV	246 / 443	13.0 [9.4; 14.8]	
Line Immunotherapy			
1st-3rd line	206 / 401	13.6 [10.0; 16.4]	p = 0.07
> 3rd line	94 / 150	10.8 [7.6; 14.3]	
*** If PDL1 done,**			
PDL1 status :			
Negative	34 / 71	16.0 [11.3; 20.5]	p = 0.57
Positive (>1%)	61 / 143	15.6 [14.2; 26.3]	
% of tumor cells PDL1			
<10%	38 / 88	16.4 [11.3; 24.0]	p = 0.52
>=10%	31 / 89	18.4 [14.3; NR]	
% of tumor cells PDL1			
<50%	48 / 117	17.1 [13.6; 24.0]	p = 0.65
>=50%	21 / 60	18.4 [11.4; NR]	
% of tumor cells PDL1			
0%	34 / 71	16.0 [11.3; 20.5]	p = 0.51
1-49%	14 / 46	NR [7.4; NR]	
50-100%	21 / 60	18.4 [11.4; NR]	

EVT Event; N Number; NR Not Reached

S9:

	EVT/ N	Median PFS [95%CI] (Months)	p
Gender			
Male	217/274	2.9 [2.4; 3.4]	p=0.57
Female	232/277	2.7 [2.2; 3.2]	
Age at diagnosis			
<= 60 years	233/284	2.5 [2.1; 2.8]	p=0.29
> 60 years	216/267	3.1[2.7; 3.5]	
Smoking			
Never smoker	136/148	2.5 [1.8; 2.8]	**p<0.0001**
Former smoker	216/269	2.8 [2.3; 3.3]	
Current smoker	81/113	3.5 [2.4; 6.2]	
Stage at diagnosis			
IA-IIIA	79/99	3.3 [2.5; 4.6]	p=0.31
IIIB-IV	361/443	2.7 [2.3; 3.0]	
Line Immunotherapy			
1st-3rd line	318/401	2.9 [2.5; 3.4]	p=0.08
> 3rd line	131/150	2.5 [1.9; 2.7]	
*** If PDL1 done,**			
PDL1 status :			
Negative	60/71	3.0 [2.1; 3.9]	**p=0.02**
Positive (>1%)	100/143	4.2 [2.8; 5.8]	
% of tumor cells PDL1			
<10%	73/88	2.9 [2.3; 3.9]	**p=0.02**
>=10%	56/89	4.7 [2.6; 7.0]	
% of tumor cells PDL1			
<50%	91/117	3.1 [2.3; 4.1]	p=0.15
>=50%	38/60	4.7 [2.5; 7.2]	
% of tumor cells PDL1			
0%	60/71	3.0 [2.1; 3.9]	p=0.08
1-49%	31/46	4.0 [2.0; 8.0]	
50-100%	38/60	4.7 [2.5; 7.2]	

EVT Event; N Number

S10:

	EVT/N	Median PFS [95%CI] (Months)	*p*
KRAS			
G12C	72/100	5.5 [2.7; 7.9]	0.47
Other	112/143	3.1 [2.5; 4.5]	
EGFR			
T790 single or multiple	30/30	1.4 [1.1; 1.9]	P<0.0001
Exon19	23/23	1.8 [1.4; 2.7]	
Exon21	25/28	2.5 [1.5; 4.3]	
other	32/35	2.8 [2.1; 5.2]	
BRAF			
V600E	14/17	1.8 [1.0; 4.6]	p=0.20
Other	14/18	4.1 [2.0; 9.0]	
MET			
Exon14 yes	17/23	4.7 [1.8; 7.8]	0.09
Exon14 no	8/10	1.3 [0.6; 6.2]	

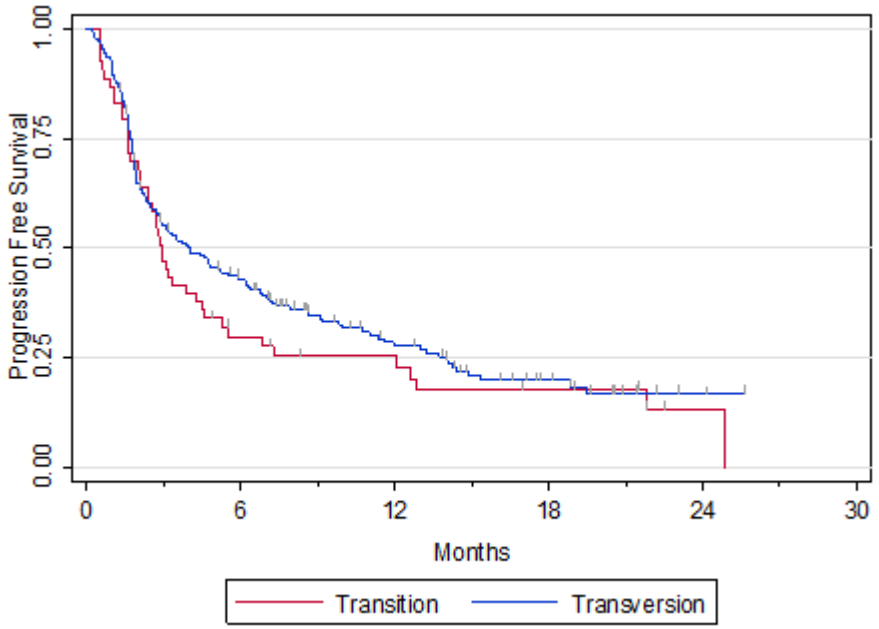
EVT Event; N Number

S11: Rate of hyperprogression

		Progression within 2 months	No Progression at 2months
	N=540	**N=212**	**N=328**
	100%	**39.2%**	**60.8%**
Type of primary mutation			
EGFR	125	56 (44.8%)	69 (55.2%)
KRAS	267	96 (36.0%)	171 (64.0%)
ALK	22	10 (45.5%)	12 (54.5%)
ROS1	7	3 (42.9%)	4 (57.1%)
BRAF	42	17 (40.5%)	25 (59.5%)
HER2	28	11 (39.3%)	17 (60.7%)
RET	16	7 (43.8%)	9 (56.3%)
MET	33	12 (36.4%)	21 (63.6%)

S12: Overall survival and Progression free survival according to KRas type of mutation: Transition vs Transversion

KRas mutation type	*N (Total=271)*	%	
Transition	*53*	22	
Transversion	*188*	78	
Missing	*30*		
	EVT / N	Median OS or PFS months [95%CI]	p
OS			
Transition	*32 / 53*	7.4 [5.8; 14.3]	0.3043
Transversion	*96 / 188*	14.3 [9.8; 17.8]	
PFS			
Transition	*44 / 53*	2.9 [2.1; 4.5]	0.2688
Transversion	*138 / 188*	4.0 [2.8; 5.9]	



S13:

	PDL1 Neg Median PFS [95%CI]	>1% Median PFS [95%CI]	*p*	Smoking Never Median PFS [95%CI]	Current or former Median PFS [95%CI]	*p*	ICI line 1st-3rd Median PFS [95%CI]	>3rd Median PFS [95%CI]	*p*	Variant	Median PFS [95%CI]	p
KRAS	3.9[1.7; 6.8]	7.2[4; 14.4]	0.01	4.6[1.6; 8.4]	3.1[2.7; 4.0]	0.98	3.2[2.7; 4.5]	3.1[1.9; 7.1]	0.66	G12C G12A G12D G12V G12S Other	5.5[2.7; 7.9] 4.4[2.1; 10] 3.2[2.4. 5.3] 1.9[1.6. 5.1] 2.1[1.1. NR] 2.8[2.0; 10.7]	0.90
EGFR	1.7[1.2; 2.7]	2.8[1.9; 7.2]	0.01	2.1[1.7; 2.7]	2.4[1.9; 3.7]	0.06	2.5[2; 3.5]	1.9[1.6; 2.6]	0.19			
BRAF	-*	-*	na	1.9[0.7; 4.1]	4.1[1.8; 7.8]	0.03	3.1[1.5; 4.8]	2.7[1.6, NR]	0.58			
HER2	-*	-*	na	2.0[1.5; 2.9]	3.4[1.6; NR]	0.04	2.9[1.8; 5.4]	2.0[1.2; .]	0.30	-*	-*	
MET	-*	-*	na	5.8[1.3; NR]	3.4[1.7; 6.9]	0.92	-*	-*	na			
ALK/ROS/RET	-*	-*	na	2.6[1.7; 4.7]	1.8[1.4; 2.2]	0.03	1.8[1.3; 3.8]	2.6[1.8; 3.7]	0.46			

-*: not enough events to perform the univariate analysis

NR Not Reached

Driver	n	RR	PFS	OS	Impact (+/-) on PFS of				Comments
					PDL1	Smoking	Nb line	Subtype	
Total		19%	2.8	13.3					Outcome consistent with registration trials for ICI
KRAS	271	26%	3.2	13.5	+	X	X	X	Clear benefit across all subgroups
EGFR	125	12%	2.1	10	+	X	X	+/-(1)	Could be considered in PDL1 + after TKIs exhaustion
BRAF	43	24%	3.1	13.6	NA	+	X	X	Could be considered in smokers
MET	36	16%	3.4	18.4	NA	X	NA	X	Could be considered after conventionnal treatment
HER2	29	7%	2.5	20.3	NA	+	X	NA	
ALK	23	0	2.5	17					
RET	16	6%	2.1	21.3	NA	-	X	NA	Poor outcome. New biomarker needed.
ROS1	7	17%	-	-					

+ : positive impact on PFS
X : non-significant impact on PFS
- : negative impact on PFS
(1) Depending on the mutation subtype, cf. table A7

S12

317x176mm (150 x 150 DPI)