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This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1703925> since 2019-06-04T14:41:27Z

Published version:

DOI:10.1093/annonc/mdz167

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Article type: original article

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

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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 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 [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]. 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 an oncogenic driver. 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; 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.

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 Nh22181405I) 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 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 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 (supplementary 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 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 (supplementary S4 and S5).

Clinical outcomes

Response rate

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, supplementary S6. Details according to mutation subtype are in supplementary table S7.

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 (supplementary 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 ($p = 0.08$). (supplementary 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%) (supplementary 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, $p = 0.27$, (supplementary S12).

PFS was significantly different across *EGFR* 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).

For *BRAF* 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, $p = 0.20$).

MET molecular alterations were found in 36 patients. Median PFS correlated neither with alteration subtype (exon 14 skipping mutation vs other *MET* alterations, $p = 0.09$), 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. (supplementary S13, S5). Main results for all cohorts are presented in supplementary S14.

Discussion

The standard of care for patients with actionable driver alterations is a targeted therapy. 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 previously reported [9]. It has been reported that *KRAS*-mutant NSCLC are more likely to express PD-1 and PD-L1 [20]. 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. 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. Recently, *STK11/LKB1* co-mutation in *KRAS*-mutant NSCLC was reported as a new predictive marker for tumor resistance to ICI therapy [21]. *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.

Concerning patients with *EGFR* mutation, the role of ICI therapy is still controversial. Recent studies showed an inverse relationship between PD-L1 expression and *EGFR* mutations. Moreover, an uninflamed tumor microenvironment is often reported in the context of oncogenic addiction [22,23]. 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 [24]. 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 [25]. 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 [26]. 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]. 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 [27]. Recently, Dudnik *et al.*

reported frequent expression of PDL1 and comparable PFS (3.7 months) in BRAF V600E mutated patients [28]. 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.

ALK, *ROS1* and *RET* translocation represent a small subgroup of NSCLC. 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 [29]. Although these data are preliminary, we do not recommend ICI as single agents in patients with ALK/ROS1/RET rearranged NSCLC.

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. 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).

ACKNOWLEDGEMENTS

We thank all participating centers for supporting this study and the eCRF team.

FUNDING

This work was supported by public funding from Toulouse University Hospital (France); and Lucerne Cantonal Hospital (Switzerland). The research was carried out with no industry support and the paper was written by the authors without editorial assistance. No grant number is applicable.

DISCLOSURE

Pr Julien Mazières reported: Consulting advisory role for Novartis, Roche/Genentech, Pfizer, BMS, E Lilly/ImClone, MSD, Astrazeneca; Research funding from Roche, BMS, Astrazeneca; Travel fees from Pfizer, Roche, BMS. Dr Martinez reported: Honoraria from Roche, BMS; Consulting advisory role from Roche BMS, Boehringer, Travel fees from BMS. Pr Barlesi reported Honoraria from Astrazeneca, Boehringer, E Lilly, Merck, MSD, Novartis, P Fabre, Pfizer, Roche, Takeda; Consulting advisory role from Astrazeneca, Boehringer, E Lilly, Merck, MSD, Novartis, P Fabre, Pfizer, Roche, Takeda; research funding from Astrazeneca, BMS, P Fabre, Roche. Dr Bironzo reported Honoraria from BMS, Boehringer. Pr Cortot reported Honoraria from Astra Zeneca, BMS, MSD, Roche, Pfizer, Novartis, Takeda; Consulting advisory role from Astrazeneca, Novartis, Pfizer, Roche; Research funding from Merck Serrono, Novartis; Travel fees from Roche, Pfizer, Astra Zeneca. Pr Couraud reported honoraria from Pfizer, Astrazeneca, MSD, Novartis, Boehringer, BMS, E Lilly, Merck Serrono, Chugai Pharma; Research funding from Roche, Pfizer, Astrazeneca, Boehringer. Dr Gounant reported Honoraria from MSD; Consulting advisory role from Astrazeneca, Roche, Boehringer, BMS, Abbvie; Travel accommodation from Pfizer. Pr Alex Drilon reported Consulting advisory role from Ignyta, Loxo, TP Therapeutics, Astrazeneca, Pfizer, Blueprint Medicines, Roche/Genentech, Takeda, Helsinn Therapeutics, BeiGene. Dr Ou reported Honoraria from Pfizer, Roche, Genentech, Takeda, Novartis, Astrazeneca, Foundation Medicine; Consulting advisory role from Pfizer, Roche, Novartis, Astrazeneca, Takeda, Foundation medicine, TP Therapeutics, Ignyta; Speakers bureau from Genentech, Astrazeneca; Takeda; Research funding from Pfizer, Roche, Astrazeneca, MedImmune, Clovis Oncology, ARIAD, Ignyta, Peregrine Pharma, GSK, Astellas Pharma, Chugai Pharma. Dr Curioni reported consulting advisory role from Roche, Boehringer, BMS, Pfizer, Astrazeneca, MSD, Takeda. Dr Neal reported consulting advisory role from Takeda, Astrazeneca, Genentech, Lilly; Research funding from Genentech, Merck, Novartis, Boehringer, Exelixis, Takeda, Nektar Therapeutics. Dr Ng Terry reported honoraria from Takeda, Ariad, Boehringer. Dr Novello reported Speakers Bureau from Astrazeneca, MSD, BMS, Roche, Pfizer, Lilly, Takeda. Dr Peled reported honoraria from Astrazeneca, Boehringer, BMS, Lilly, MSD, Novartis, Pfizer, Roche, NovellusDx, FMI, Gaurdants360; consulting advisory role from Astrazeneca, Boehringer, BMS, Lilly, MSD, Novartis, Pfizer, Roche, NovellusDx, FMI, Gaurdants360; Research funding from Astrazeneca, Boehringer, BMS, Lilly, MSD, Novartis, Pfizer, Roche, NovellusDx, FMI, Gaurdants360; Travel fees from Astrazeneca, Boehringer, BMS, Lilly, MSD, Novartis, Pfizer, Roche, NovellusDx, FMI, Gaurdants360. Dr Rothschild reported Consulting advisory role from BMS, Astrazeneca, Lilly, Boehringer, Eisai, Roche, Novartis, Merck, MSD, Astellas, Bayer, Pfizer, Takeda; Research funding from Boehringer, Astrazeneca, BMS, Eisai, Merck, Expert Testimony from Roche, Astrazeneca, BMS, Roche, Lilly, Astrazeneca, Amgen.

Dr Terry Ng reported Honoraria from Ariad, consulting advisory role from Boehringer.
Dr Veillon reported honoraria and consulting advisory role from Boehringer, MSD, BMS, Astrazeneca; research funding from Roche, BMS, Takeda, Abbvie, Pfizer, Merck. Dr Wakelee reported honoraria from Novartis, Astrazeneca; research funding from Genentech, Pfizer, Lilly, Celgene, astrazeneca, exelixis, Novartis, Clovis, Xcovery, BMS, Gilead, Pharmacyclics, ACEA biosciences; travel fees from Astrazeneca. Dr Wiesweg reported travel fees from Illumina, Astrazenca. Dr Zhu reported Stock from TP therapeutics; Honoraria from Astrazeneca, consulting advisory role from Astrazeneca, Takeda, TP therapeutics; speakers bureau from Astrazeneca, Roche. Dr Alesha A Thai, Dr Oliver Gautshi, Dr Van den Heuvel, Dr Lattuca Truc, Amelie Lusque, Dr Céline Mascaux, Dr Laurent Mhanna, Julie Milia, Dr Laura Mezquita, Dr Sanjay Popat, Dr Rafael Rosell, Dr Schouten, Dr Ross Camidge, Dr Gérard Zalcman, Dr Ben Solomon, Dr Martin Früh, Dr Benjamin Besse did not report any Conflict of Interest

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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

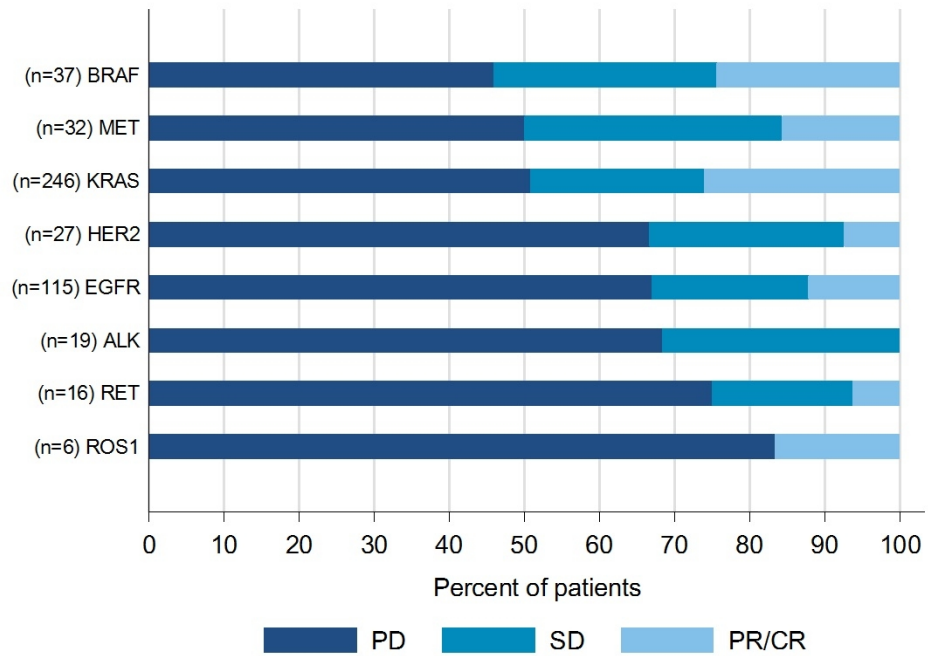


Figure 1: Best response to ICI according to RECIST criteria (PD Progressive disease, SD Stable disease, PR Partial response, CR Complete Response).

194x141mm (150 x 150 DPI)

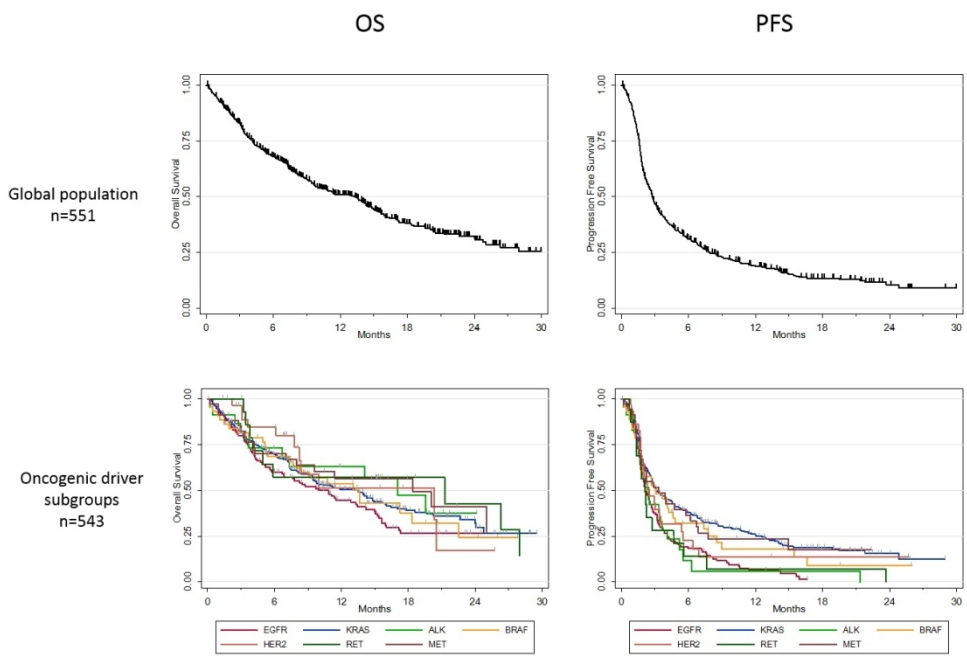


Figure 2: Overall survival (on the left) and progression-free survival (on the right) in the whole cohort (upper figures) and in each subgroup (lower figures).

236x158mm (150 x 150 DPI)

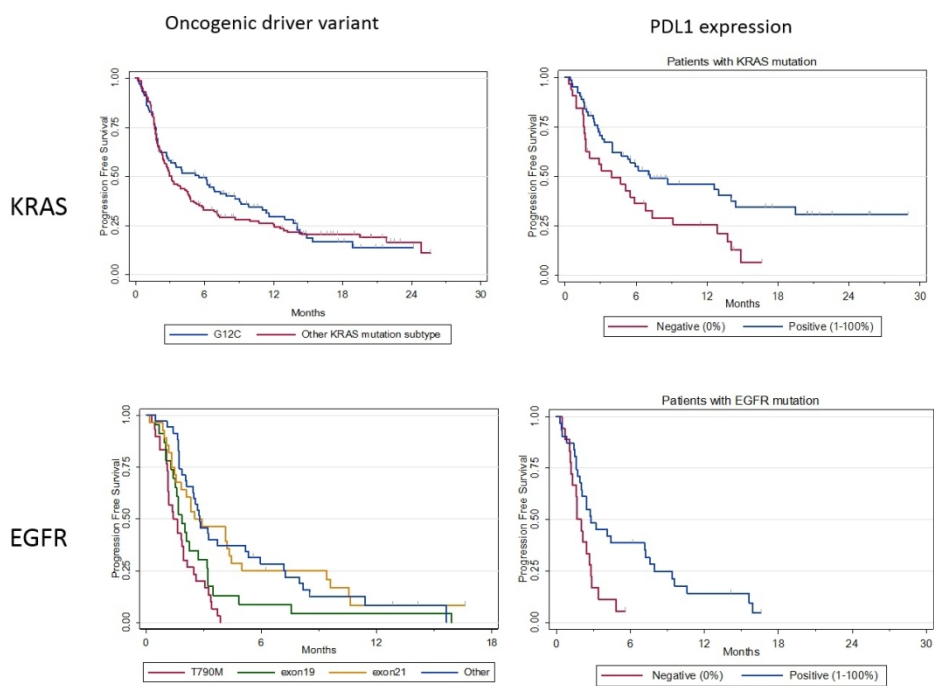
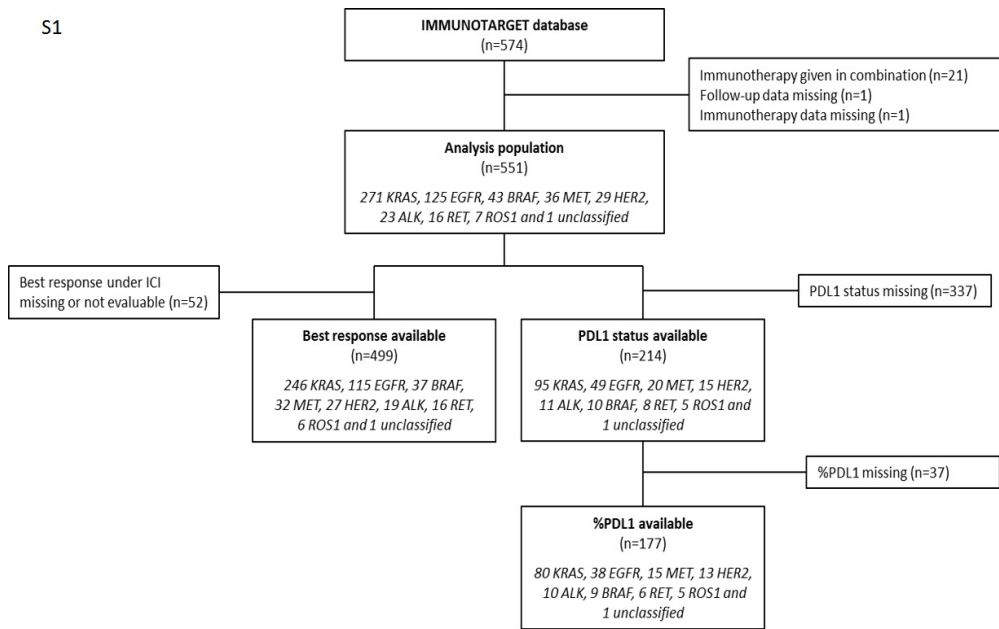


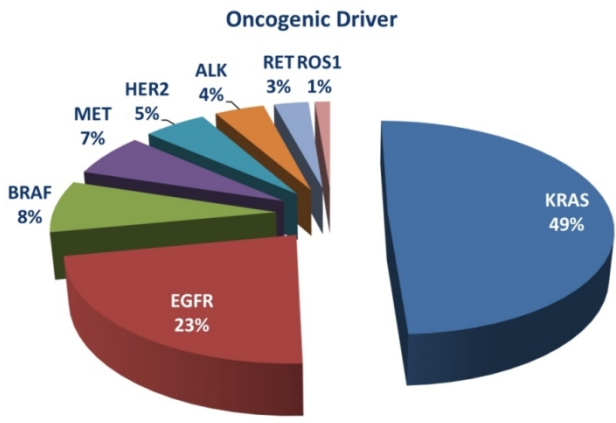
Figure 3: PFS according to oncogenic drivers' variants and PDL1 expression.

229x161mm (150 x 150 DPI)

S1



207x130mm (150 x 150 DPI)



	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

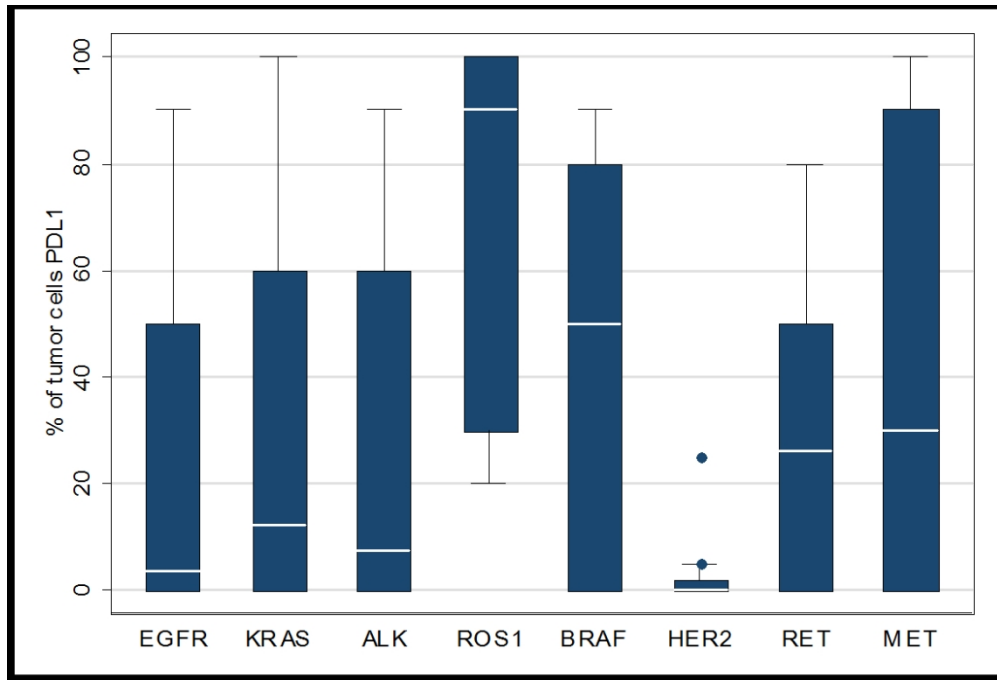
249x141mm (150 x 150 DPI)

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		
1 st line	30	5.4
2 nd line	227	41.2
3 rd line	144	26.1
4 th line	73	13.2
>4 th Line	77	14
Duration of the line (months)		
n=485		
Median	2.1	
Range	0.03-27.4	
missing	66	
Number of injections n=470		
Median	5	
Range	1-68	
Missing	81	

S4:

	EGFR		KRAS		ALK		BRAF		ROS1		HER2		RET		MET	
	N=125		N=271		N=23		N=43		N=7		N=29		N=16		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						Missing
	CR/PR*		SD		PD		
	N	%	N	%	N	%	
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-III A	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

S10:

	EVT/N	Median PFS [95%CI] (Months)	<i>p</i>
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

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-III A	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

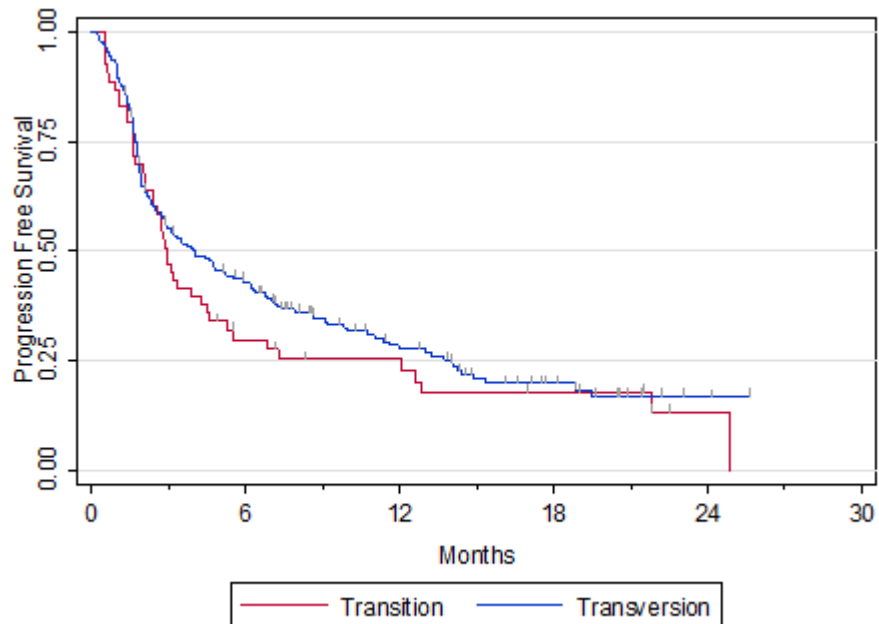
S11: Rate of hyperprogression

		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			Smoking			ICI line			Variant	Median PFS [95%CI]	p
	Neg Median PFS [95%CI]	>1% Median PFS [95%CI]	p	Never Median PFS [95%CI]	Current or former Median PFS [95%CI]	p	1 st -3 rd Median PFS [95%CI]	>3 rd 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	5.5[2.7; 7.9]	0.90
										G12A	4.4[2.1; 10]	
										G12D	3.2[2.4; 5.3]	
										G12V	1.9[1.6; 5.1]	
										G12S	2.1[1.1; NR]	
										Other	2.8[2.0; 10.7]	
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 conventional treatment
HER2	29	7%	2.5	20.3	NA	+	X	NA	
ALK	23	0	2.5	17					Poor outcome. New biomarker needed.
RET	16	6%	2.1	21.3	NA	-	X	NA	
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)