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# Immune checkpoint inhibitors re-challenge efficacy in non-small-cell lung cancer patients

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## Abstract

**Background** Immune checkpoint inhibitors (ICPis) re-challenge could represent an attractive option in non-small-cell lung cancer (NSCLC), yet no sufficient data supporting this strategy are available. This retrospective, observational, multicentre, national study explored the efficacy of anti-PD1/PDL1 re-challenge in advanced NSCLC patients looking for potential clinical features associated with greater outcomes.

**Methods** We retrospectively collected data from 144 advanced NSCLC patients, re-challenged with ICPis following  $\geq 12$  weeks of discontinuation. The progression-free survival (PFS) and overall survival (OS) were calculated from first or second ICPi initiation to disease progression (PFS1, PFSR), death, or last follow-up (OS1, OSR), respectively.

**Results** The median age was 63 years [IQ: 58–70], most patients being male (67%), smokers (87%), adenocarcinomas (62%) and stage IV at diagnosis (66%). The best response at re-challenge was not associated with that achieved under the first ICPi ( $P = 1 \cdot 10^{-1}$ ). The median PFS1 and PFSR were 13 [95%CI: 10–16.5] and 4.4 [95%CI: 3–6.5] months, respectively. The median OS1 and OSR were 3.3 [95%CI: 2.9–3.9] and 1.5 [95%CI: 1.0–2.1] years, respectively. Longer PFSR and OSR were found in patients discontinuing first ICPi because of toxicity or clinical decision, those not receiving systemic treatment between the two ICPis, and those with good ECOG performance status (PS) at re-challenge. Only the ECOG PS proved to impact outcomes at multivariate analysis.

**Conclusion** Patients discontinuing first ICPi because of toxicity or clinical decision, those able to maintain a treatment-free period, and those with good ECOG PS may be potential candidates for re-challenge.

**Keywords:** NSCLC, immune checkpoint inhibitors, re-challenge, selection criteria, efficacy

## Introduction

Immune checkpoint inhibitors (ICPis) have completely changed the treatment algorithm of locally advanced and/or metastatic non-small-cell lung cancer (NSCLC) due to their impressive results in terms of survival. Currently, four ICPis (pembrolizumab, nivolumab, atezolizumab, and durvalumab) have been approved, and almost every NSCLC patient receives at least one of these within the first three lines of therapy. Several patients experience long-term clinical benefits from these new drugs, through most patients eventually discontinue ICPis due to disease progression, toxicities, or trial designs imposing discontinuation after a given treatment period. Primarily in patients achieving a long-term response without clinically meaningful toxicities, ICPi re-challenge could be an attractive option, with chemotherapy being the only possible alternative in these patients. This strategy already entered into the clinical practice for advanced melanoma patients enabled to be re-challenged with the anti-cytotoxic T lymphocyte antigen 4 (anti-CTLA4) ipilimumab, or to switch among anti-programmed cell death 1 (PD1)/programmed cell death ligand 1 (PDL1) and anti-CTLA4 agents.<sup>1-8</sup>

However, little is known about the efficacy and safety of re-challenge with anti-PD1/PDL1 agents in NSCLC patients, and the literature evidence is limited to two prospective studies investigating this issue in their post-hoc analysis. The Checkmate 153 study explored the clinical benefits of a fixed duration (one year) of nivolumab in second-line versus continuous treatment. In the fixed-duration arm, 34 advanced NSCLC patients progressed during the surveillance period and were retreated with the same drug. The median time between progression and nivolumab re-induction was 0.6 months, with a median duration of retreatment of 3.8 months.<sup>9</sup> In the Keynote 010 study, PD-L1 positive ( $\geq 1\%$ ) pre-treated advanced NSCLC patients were randomized to receive two different schedules of pembrolizumab or docetaxel. Overall, 14 patients received a second pembrolizumab course, with most of them (78%) exhibiting either partial response or stable disease.<sup>10,11</sup> . Recently, the UNIVOC study retrospectively analysed French NSCLC patients that received an ICPi retreatment after a discontinuation period from nivolumab of at least 6 weeks. These represented about 14% (1517 out of 10452) of the population treated with a first course of nivolumab including some patients that resumed the ICPis discontinued without any intercalated treatment (74%) and some other that received an ICPis re-challenge after a chemotherapy failure (26%). The median overall survival (OS) from re-challenge was 15 months for patients receiving a second course of PD-1 inhibitor after a treatment-free interval and 18.4 months for those who performed an intercalated chemotherapy. Interestingly,

median OS was significantly longer in patients with an initial nivolumab treatment duration longer than 3 months. However, no information were reported about the nivolumab discontinuation reason, patients' clinical features such as the ECOG PS and the retreatment tolerance. Consequently, it was not possible to know how selecting patients to these strategy according to clinical characteristics<sup>12</sup>. Concerning the safety, two large retrospective studies investigated the toxicity after resuming anti-PD1 agents in solid cancer patients, revealing that 50–55% of patients experienced an immune-related AEs (irAEs) of any grade at anti-PD1 resumption.<sup>13,14</sup> Of note, whereas the Simonaggio et al. study enrolled only 15 (16%) lung cancer patients, no thoracic cancer patients were included in the Pollack et al. study. Despite these encouraging data, anti-PD1/PDL1 re-challenge efficacy is still a matter of debate, owing to the lack of prospective studies specifically addressing this issue. Therefore, we have retrospectively collected a national cohort of advanced NSCLC patients who underwent anti-PD1/PDL1 re-challenge during their disease course after a discontinuation period of at least 12 weeks. This study sought to explore the potential efficacy of anti-PD1/PDL1 re-challenge in NSCLC patients and to possibly identify potential clinical features associated with greater outcomes.

## **Methods**

### **Study design**

This was a retrospective, observational, multicentre, national study aimed at collecting data of advanced NSCLC patients who benefited from an ICPI re-challenge during their disease course. It was conducted in according to the principles of the Declaration of Helsinki and in compliance with the European Regulation (EU) 2016/679, repealing the Directive 95/46/EC about General Data Protection Regulation. The patients were fully informed in understandable terms about the study's objectives and nature of the information collected. Likewise, they were informed about their right to object at any time to their data exploration. The study was registered as NCT04069663. This manuscript was written in accordance with the STROBE statement available in appendix A.

### **Patients**

We retrospectively collected the clinical data of advanced NSCLC patients followed up at 26 institutions. As per inclusion criteria, patients: 1) had a diagnosis of advanced NSCLC (stages III–IV according to the 7<sup>th</sup>–8<sup>th</sup> TNM classification)<sup>15</sup> at the first ICPI initiation; 2) received at least two lines of

anti-PD1/PDL1 agents during their disease course; 3) underwent an anti-PD1/PDL1 re-challenge after discontinuing the first ICPI for at least 12 weeks because of toxicity, disease progression, or clinical decision. Concerning this latter reason, physicians decided treatment withdrawal despite disease control and absence of toxicities, considering the long-term benefit achieved or on account of patients' demands. Moreover, 4) patients harbouring a sensible *EGFR* or *ALK* alteration had to have received every target agent regularly reimbursed before initiating the first ICPI. Patients were treated according to their own physician's decision. Radiological assessments were locally performed and their interpretation was done according to the local practice. No imaging central revision was required. Information about PD-L1 status was collected when available. De-identified clinical data were then centrally collected through case report forms (CRF) to the University Hospital of Grenoble (France, CNIL n° 2205066 v 0), where they were merged and exploited for statistical analysis.

### **Statistical analysis**

Baseline characteristics were expressed as means and standard deviations or medians and interquartile ranges (IQR) for continuous variables and as frequencies and percentages for categorical variables. Qualitative variables were compared using the chi-squares test. The overall response rate (ORR) was defined as the percentage of complete and partial responses obtained as best response, while the disease control rate (DCR) included the ORR and percentage of achieved stable disease. Median progression free survival under the first anti-PD1/PDL1 (PFS1) was calculated from the first ICPI administration to disease progression or censored at the next treatment initiation. Likewise, the median PFS under re-challenge (PFSR) was defined as the time from beginning of re-challenge to disease progression or death and was censored at the last follow-up. The time to treatment failure (TTF1) was the time from first anti-PD1/PDL1 administration to treatment discontinuation of any cause confounded. Overall survival from the first anti-PD1/PDL1 (OS1) comprised the time between first ICPI initiation to last follow-up or death any cause confounded. Conversely, the OSR was calculated from re-challenge initiation. Survival curves were obtained using the Kaplan–Meier method.<sup>16</sup> Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CI) in the subgroup analysis for the following variables: gender, smoking habit, stage at diagnosis, histology, ECOG PS, metastatic sites, treatment line, ICPI type, discontinuation reason and systemic treatment between the two ICPIs. Variables with a p value  $\leq 0.20$  in univariate Cox regression analysis

were entered into the multivariate model.<sup>17</sup> The  $\alpha$  Type I error rate  $\leq 0.05$  was considered significant for the final model. Missing data were clearly indicated in the population description and imputed elsewhere by the median value (for quantitative variables) or the most common level (for qualitative variables) in the Cox models. The statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

## Results

### Study population clinical characteristics

We retrospectively collected data on 144 patients with a diagnosis of advanced NSCLC between 2010 and 2018, all of whom met the eligible criteria to enter the study. The main patient characteristics have been displayed in table A and figure A. The median follow-up from the first ICPi administration was 28.4 months [IQR 25–75%: 17.5–37.2] and 6.6 months [IQR 25–75%: 3.2–14.] from re-challenge. Most patients received the first anti-PD1/PDL1 treatment in the first or second-line (66%) setting, and the second ICPi round in the third- or later-line (79%) (table B). To note, no patient received either the first or the second course of ICPis for a locally advanced disease. Most of patients received the anti-PD1/PDL1 as monotherapy and few of them performed a combination regimen with chemotherapy (2 patients at first ICPis round and 2 at re-challenge), antiangiogenic (1 patient at re-challenge) or anti-CTLA4 agents (4 patients at first ICPis round and 1 patient at re-challenge). In both the first ICPi course and re-challenge, patients preferentially received an anti-PD1 agent (88% and 94%, respectively), without any difference between the two settings regarding brain metastasis or ECOG PS at the time of anti-PD1/PDL1 beginning. The median TTF1 was 6.3 months [IQR 25–75%: 2.9-13.1]. Most patients discontinued the first ICPi because of disease progression (40%) or toxicity (40%), whereas 20% withheld the drug due to clinical decision. In this last group, 82% (23/28) of patients completed at least one year of ICPis. The anti-PD1/PDL1 withdrawal reason was more imbalanced in favour of disease progression (58% of cases) at re-challenge compared to the first ICPi course, wherein most patients discontinued because of toxicity or clinical decision (40% and 20%, respectively). Most of patients (57%) did not receive any systemic treatment between the two ICPis rounds being the first ICPis withdrawal due to toxicity or clinical decision in most of cases (88%). Conversely, 43% of the study population received one or more intercalated lines of chemotherapy and, in this group, the disease progression was the main cause of the ICPis discontinuation (77%).

### **Re-challenge safety**

Adverse events (AEs) during the first ICPis course and at re-challenge are detailed in Table SA. 19% (n= 27) of the entire cohort experienced a grade  $\geq$  III toxicity during the first ICPis round, more often due to skin toxicities (6/27), pneumopathy (5/27) and colitis (4/27). All of them discontinued the treatment because of toxicity and in four cases they experienced a serious AE during the re-challenge. In particular, the toxicity showed during the first ICPis recurred in two cases while two patients had a completely new AE. No patients discontinuing the first ICPis because of disease progression or clinical decision showed serious AEs, but six patients experienced a grade  $\geq$  III AEs at time of re-challenge. Globally, nine patients (6% of the entire cohort) reported a serious AEs under the re-challenge.

### **Response to anti-PD1/PDL1 re-challenge**

Higher ORR and DCR values were found during the first anti-PD1/PDL1 treatment compared to those obtained during re-challenge (50% versus 16%,  $P < 1 \cdot 10^{-5}$  and 76% versus 47%,  $P < 1 \cdot 10^{-5}$ , respectively). Indeed, a higher percentage of patients presenting disease progression as best response was observed over anti-PD1/PDL1 re-challenge compared to the first ICPi round (38% versus 18%) (figure B). Of note, the best response achieved during re-challenge was not associated with that obtained during the first anti-PD1/PDL1 round, nor was there an association between the response during re-challenge and reason for first ICPi discontinuation. Consistent results were obtained even excluding those patients that discontinued the first ICPis due to toxicity without experiencing a disease progression before the re-challenge representing 18% of the whole population (ORR 44% versus 13% and DCR 68% versus 44% during the first ICPis and at re-challenge respectively and no associations found).

### **Progression free survival under re-challenge**

At analysis, 94 (65%) patients experienced disease progression under re-challenge. Among patients censored for the PFSR analysis, 39 were still on anti-PD1/PDL1 treatment with a median duration of 5.8 months [IQ: 25–75%: 2.1–10.4]. The median PFS1 and PFSR were 13 months [95% CI: 10–16.5] and 4.4 months [95% CI: 3–6.5], respectively (figure S1).



According to the univariate analysis (table C), the factors positively impacting the PFSR were first ICPI discontinuation because of toxicity or clinical decision (toxicity: 5.1 months [95% CI: 3.3–18]; clinical decision: 6.5 months [95% CI: 2.8–11.9]; disease progression: 2.9 months [95% CI: 2.0–4.4]), no systemic treatment between the two ICPI rounds, and re-challenge in early line settings. Moreover, patients with a better ECOG PS, low metastatic site number, and without brain metastasis exhibited a longer PFSR, whereas bone metastasis exerted a negative impact. Of note is that no differences were found in terms of PFSR according to TTF1 duration (three TTF1 cut-offs considered: <3 months, ≥3 months and <6 months or ≥6 months).

After having entered all these factors into the multivariate model, only the ECOG PS at re-challenge initiation was confirmed to impact the PFSR.

### **Overall survival**

At the time of analysis, 55 (38%) patients had died. The median OS1 was 3.3 years [95% CI: 2.9–3.9], and median OSR was 1.5 years [95% CI: 1.0–2.1] (figure S2). The swimmer plot in figure S3 details the OS1 for each patient. The median OSR turned out to be even longer in patients discontinuing the first ICPI due to toxicity or clinical decision (toxicity: 2.1 years [95% CI: 1.4–NR]; clinical decision: 1.6 years [95% CI: 0.5–NR]; disease progression: 1.0 year [95% CI: 0.5–1.6]), those not receiving systemic treatment between the two ICPI rounds (intercalated therapy: 1.4 years [95% CI: 0.6–1.6]; : no intercalated therapy 2.1 years [95% CI: 1.1–NR]), and those with a better ECOG PS at re-challenge (ECOG PS 0: NR [95% CI: 2.1 years –NR]; ECOG PS 1: 1.4 year [95% CI: 0.2–2.1]; ECOG PS ≥2: 1.1 years [95% CI: 0.7–1.6]), according to the univariate analysis (table D). Again, no differences were found in terms of OSR according to the TTF1 duration (three TTF1 cut-offs considered as for the PFSR analysis). In the multivariate model, only the ECOG PS was demonstrated to impact OS upon re-challenge.

### **Discussion**

According to our results, patients experienced better outcomes upon the first ICPI administration versus re-challenge in terms of ORR (50% versus 16%) and PFS (13 versus 4.4 months). Poor data are available in literature to provide a valid comparator. However, these results at re-challenge are pretty interesting if compared with chemotherapy in ICPIs progressing patients in retrospectives

analysis showing a median PFS ranging from 2.0 to 4.7 months and a ORR from 16% to 39% with a single-agent treatment<sup>18,19</sup>. Moreover, the efficacy of anti-PD1/PDL1 agents at re-challenge seems consistent with data about nivolumab and pembrolizumab in pre-treated NSCLC patients enrolled in Phase II and III clinical trials revealing a median PFS ranging from 2.3 to 4.0 months.<sup>10,20-23</sup> These data suggest that the efficacy of anti-PD-1 and anti-PD-L1 may not be affected by the previous ICPI treatment. Therefore, immunotherapy re-challenge may represent an attractive and less toxic alternative to chemotherapy in selected patients.

Considering survival data (3.3 years from first ICPI, and 1.5 years from re-challenge), these probably reflect a selected population likely to exhibit a particularly indolent disease and having a survival longer than expected. However, while these patients actually exist, it appears crucial to us to be able to identify them. To note, clinical characteristics at baseline were quite consistent with those expected in the general advanced NSCLC population, considering the published literature data. Nevertheless, several factors reflecting the disease history were found to impact the outcomes under re-challenge in our study. For instance, a longer PFS and OS with anti-PD1/PDL1 re-challenge was achieved in patients who discontinued the first ICPI due to toxicity or clinical decision (in most cases because of long-term benefit) compared to progressive patients. Moreover, patients who did not require a chemotherapy regimen between the two ICPIs courses being able to maintain a treatment-free period, and those with a better ECOG PS at the re-challenge experienced better outcomes as well. Interestingly, the best response and median TTF under the first ICPI round did apparently not affect outcomes under re-challenge, being thus not particularly useful for patient selection according to our study. These results are consistent with the UNIVOC trial reporting a median OS of 15-18 months from re-challenge but, in that case, patients that performed an intercalated chemotherapy showed a longer survival<sup>12</sup>. To note, in our study, we included patients with a longer ICPI discontinuation period (12 versus 6 weeks as per inclusion criteria) possibly overestimating the survival of patients able to keep a treatment free period. Globally, our results are in fact not surprising given that patients with these characteristics are supposed to have a more favourable prognosis. To note, most of patients that were able to keep a treatment-free period are also those who discontinued the first ICPIs because of toxicity or clinical decision suggesting a more indolent disease. Therefore, given the absence of a comparator arm we cannot estimate the clinical benefit linked to the re-challenge strategy compared to a standard chemotherapy. We cannot actually exclude that re-challenge did not specifically change

the disease course of these patients which would have been favourable even with another treatment type. Indeed, in the multivariate model, only the ECOG PS at re-challenge was proven to independently impact either PFS or OS at re-challenge. However, this could also have been caused by the small-sized study population given the number of variables considered in the multivariate analyses. Nevertheless, we can certainly conclude that only patients in good clinical condition should be considered for this strategy. Indeed, despite these agents' good safety profile, the rather modest benefits obtained upon re-challenge in deteriorated-health patients should discourage physicians from adopting this strategy in this population.

Finally, according to our study, re-challenge seems safe counting only 6% of serious (grade  $\geq$  III) adverse events. Despite the short follow-up from re-challenge did not allowed a clear conclusion about the long-term safety of this strategy, we can speculate on a good early-onset toxicity profile that need to be confirmed in a prospective manner.

According to the European Medicine Agency, anti-PD1/PDL1 agents represent the upfront treatment (with or without chemotherapy) for advanced NSCLC and can be prescribed as monotherapy in further lines. Additionally, durvalumab (anti-PD-L1) was recently approved in a locally advanced setting for PD-L1-positive patients. These drugs may actually confer impressive clinical benefits in term of survival. In the Keynote 001 study, 18% of patients receiving pembrolizumab in an advanced setting were still alive at 5 years.<sup>24</sup> Likewise, second-line nivolumab was estimated to provide a 5-year OS rate of 16%.<sup>25</sup> Thus, it seems clear that these drugs are able to shape the anti-tumour immune response more efficiently in some patients than in others; in these latter, a reconditioning strategy may prove to be an interesting option. This therapeutic approach has already been successfully applied in advanced melanoma patients enabled to be re-treated with the same anti-CTLA4 or to receive a sequential administration of anti-CTLA4 and anti-PD-1/PD-L1 agents.<sup>1-8</sup> However, only patients who achieve an objective response to the first ICPI lasting  $\geq$ 3 months without experiencing Grade III or IV AEs can be considered for re-challenge according to results of prospective trials. We are, nevertheless, not allowed to extrapolate these strategies towards lung cancer patients, because only little is known about the efficacy and safety of anti-PD1/PDL1 re-exposition in NSCLC patients. The literature data are insufficient to provide answers to these questions.<sup>9-11</sup> Further prospective clinical trials designed to investigate this issue concerning different tumour types (NCT03526887, NCT03847649, NCT02743819, NCT03262779, NCT03041181,

NCT03847649, NCT03334617, and NCT03469960) are either already ongoing or scheduled to start shortly. These trials' results, once available, will certainly help better define both the clinical benefits and criteria for improving patient selection.

Our report provides a snapshot of re-challenge efficacy in a large real-world population of advanced NSCLC patients. Our results are complementary to those already available in the literature providing new insights on patient selection criteria but also on PFS and response rate under re-challenge. Moreover, we included some patients receiving the first ICPI course as upfront treatment which will become an increasingly common situation as regimens combining chemotherapy and immunotherapy recently reached the front-line setting regardless of PD-L1 expression. However, the well-known limitations of data retrospectively collected along with radiological assessments that were locally assured (schedule and interpretation) without a central review must be taken into account. Moreover, the survival analyses were limited due to the low event number registered (38% of the entire cohort), likely on account of the inherently selected population. Finally, given the low number of PD-L1 test performed in the clinical practice during the study period, we were not able to take into account this variable for multivariate analyses. As currently all patients are tested, it could be interesting to evaluate whether the PD-L1 status affects the re-challenge outcomes. Therefore, this report contributes to improving our knowledge about anti-PD1/PDL1 re-treatment in NSCLC patients, providing interesting insights that must still be validated via currently ongoing prospective clinical trials.

## **Conclusion**

In conclusion, anti-PD1/PDL1 re-challenge could constitute a therapeutic option in selected NSCLC patients, particularly those discontinuing the first ICPI because of toxicity or clinical decision, those able to maintain a treatment-free period between the two ICPI rounds, and those maintaining a good ECOG PS at re-challenge. These patients are most likely to be potential candidates for this re-challenge strategy. Contrarily, frail patients with deteriorated general health conditions should not be considered for anti-PD1/PDL1 re-challenge.

## **Contributors**

EG performed literature research. EG, ACT, and MGL contributed to study design and data collection, analysis, and interpretation. EG was in charge of manuscript writing. All other co-authors equally

contributed to data collection, manuscript revision and approved the final version of the submitted manuscript.

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This study was conducted with the financial support of Bristol-Myers Squibb (BMS) that, however, was not involved in study design, data collection, analysis or interpretation of data. Thus, authors have had full access to all data collected in the study and they had the final responsibility for the decision to submit this article for publication.

### **Declaration of interests**

EG received personal fees from Astrazeneca, Roche, Merck Sharpe and Dohme and Bristol-Myers Squibb, as well as research grant from Bristol-Myers Squibb outside the submitted work. CD received personal fees from Roche, Bristol-Myers Squibb, Merck Sharpe and Dohme, Astrazeneca, Pfizer, Takeda, and Boeringher Ingelheim outside the submitted work. RV received personal fees from Pfizer, Merck Sharpe and Dohme, Bristol-Myers Squibb, Astrazeneca, Roche, Takeda, Abbvie, Merck-Serono, and Astellas outside the submitted work. ED received personal fees from Roche, Bristol-Myers Squibb, Astrazeneca and Merck Sharpe and Dohme and research grant from Roche outside the submitted work. MP received personal fees from Roche, Genentech, Eli Lilly, Pfizer, Boehringer-Ingelheim, Clovis Oncology, Merck Sharpe and Dohme, Bristol-Myers Squibb, Novartis, Pierre Fabre, Astrazeneca, Takeda, Amgen, Chugai, as well as a research grant from Roche, AstraZeneca, Chugai, Takeda outside the submitted work. FB received personal fees from Astrazeneca, Bayer, Bristol-Myers Squibb, Boehringer-Ingelheim, Eli Lilly Oncology, F. Hoffmann-La Roche Ltd, Novartis, Merck, Merck Sharpe and Dohme, Pierre Fabre, Pfizer and Takeda, as well as non-financial support from Astrazeneca, BMS, Merck, Pierre Fabre and Roche outside the submitted work. VG received personal fees from Astrazeneca, Roche, Pfizer, Boehringer, Bristol-Myers Squibb, Merck Sharpe and Dohme, Takeda, Chugai and Novartis outside the submitted work. BD received personal fees from Roche, Oxyvie, Pfizer, and Astrazeneca outside the submitted work. FG received personal fees from Astrazeneca, Boehringer Ingelheim, Merck Sharpe and Dohme, Bristol-Myers Squibb, and Roche outside the submitted work. LM received personal fees from Roche Diagnostics, Bristol-Myers Squibb, Tecnofarma, Roche, Astrazeneca and Chugai, as well as a research grant from Astrazeneca outside the submitted work. DMS received personal fees from Roche, Merck Sharpe and Dohme, Bristol-

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## Appendix A

STROBE Statement—Checklist of items that should be included in reports of **cohort studies**. The position of items in the text is indicated within brackets next to each item.

	<b>Item</b>	
	<b>No</b>	<b>Recommendation</b>
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (Abstract session→ Question)
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found (Abstract session→ Methods and Results)
<b>Introduction</b>		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (Introduction session)
Objectives	3	State specific objectives, including any prespecified hypotheses (Introduction session→Last 3 lines)
<b>Methods</b>		
Study design	4	Present key elements of study design early in the paper (Methods session→ study design)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (Methods session→ Patients and Results session→ Study population clinical characteristics)
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (Methods session →Patients)
		(b) For matched studies, give matching criteria and number of

exposed and unexposed (Not applicable)

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Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (Methods session → Objectives and statistical analysis)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (Methods session → Objectives and statistical analysis)
Bias	9	Describe any efforts to address potential sources of bias (Not applicable)
Study size	10	Explain how the study size was arrived at (Not applicable)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (Methods session → Objectives and statistical analysis)
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (Methods session → Objectives and statistical analysis)
		(b) Describe any methods used to examine subgroups and interactions (Methods session → Objectives and statistical analysis)
		(c) Explain how missing data were addressed (Methods session → Objectives and statistical analysis)
		(d) If applicable, explain how loss to follow-up was addressed (not applicable because no patient was lost at follow-up)
		(e) Describe any sensitivity analyses (Methods session → Objective and statistical analysis)

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## Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (Results session→ Study population clinical characteristics)
		(b) Give reasons for non-participation at each stage (Results session→ Study population clinical characteristics)
		(c) Consider use of a flow diagram (Not applicable, Figure 1 resume study population characteristics)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (Results session→ Study population clinical characteristics and Figure 1)
		(b) Indicate number of participants with missing data for each variable of interest (Results session→ Study population clinical characteristics and Tables 1 and 2)
		(c) Summarise follow-up time (eg, average and total amount) (Results session→ Study population clinical characteristics)
Outcome data	15*	Report numbers of outcome events or summary measures over time (Results session→ Response to anti-PD1/PDL1 re-challenge, Progression free survival under re-challenge, Overall survival)
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (Results session→ Progression free survival under re-challenge, Overall survival, Figure S1, Figure S2, Table 3, Table 4)
		(b) Report category boundaries when continuous variables were

		categorized (Results session → Table 1 and 2)
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (Not applicable)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (Results session→ Progression free survival under re-challenge, Overall survival, Table 3, Table 4)
<b>Discussion</b>		
Key results	18	Summarise key results with reference to study objectives (Discussion session→ first part)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (Discussion session → Last part)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (Discussion session→ intermediate part)
Generalisability	21	Discuss the generalisability (external validity) of the study results (Discussion session → Intermediate part)
<b>Other information</b>		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (Role of founding source session)

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

**Table A: Study population clinical features (n=144)**

Feature	
<b>Age</b>	63 years [58–70]
<b>Gender</b>	
Male	97 (67)
Female	47 (33)
<b>Smoking habit (MD=9)</b>	
Current	55 (41)
Former	70 (52)
Never	10 (7)
<b>Stage at diagnosis</b>	
I-II	15 (10)
III	34 (24)
IV	95 (66)
<b>Histology</b>	
Non-squamous	90 (62)
Squamous	47 (33)
Other	7 (5)
<b>PDL1 status (MD=92)</b>	
Negative	9 (17)
≥ 1%	43 (83)
≥ 25%	22 (42)
≥ 50%	21 (40)
<b>Molecular alterations*</b>	
At least one molecular alteration	53
<b>Treatments between ICPis</b>	
Chemotherapy	62 (43)
Number of lines	1 [1–4]
Radiotherapy	26 (18)

Qualitative variables were expressed as n (%) and quantitative variables as median (IQR 25%-75%). MD=missing data. PDL1= Programmed death-ligand 1. ICPis= immune checkpoint inhibitors.  
 \*Information collected about the following molecular tests: EGFR, ALK, KRAS, MET, STK11, BRAF, ROS1, FGFR, HER2, RET. To note, they were not systematically assessed on the entire cohort. In particular, referring to the number of patients tested: EGFR+ 3/89; ALK+ 0/83; KRAS+ 36/88; MET+ 4/55; STK11+ 0/13; BRAF+ 6/78; ROS1+ 0/70; FGFR+ 0/19; HER2+ 2/66; RET+ 2/22.

**Table B: Study population clinical features at first anti-PD1/PDL1 round and at re-challenge (n=144)**

Feature	First anti-PD1/PDL1	Re-challenge	P value
<b>ECOG PS</b>	(MD=3)	(MD=4)	
0-1	124 (88)	115 (82)	
≥ 2	17 (12)	25 (18)	1·10 <sup>-1</sup>
<b>Brain MTS</b>	(MD=1)	(MD=1)	
Yes	24 (17)	33 (23)	
No	119 (83)	110 (77)	1·10 <sup>-1</sup>
<b>Treatment line</b>			
First line	19 (13)	6 (4)*	
Second line	76 (53)	24 (17)	
Third line	36 (25)	39 (27)	
Further lines	13 (9)	75 (52)	
<b>ICPi type</b>			
Anti-PD1	126 (88)	136 (94)	
Anti-PDL1	18 (12)	8 (6)	3·10 <sup>-2</sup>
<b>Discontinuation reason</b>		(MD=2)	
Disease progression	58 (40)	83 (58)	
Toxicity	58 (40)	18 (12)	
Clinical decision	28 (20)	4 (3)	1·10 <sup>-5</sup>
Treatment ongoing	0 (0)	39 (27)	
Qualitative variables were expressed as n (%) and quantitative variables as median (IQR 25%-75%). MD=missing data. PS=performance status. MTS=metastasis. ICPi=immune checkpoint inhibitor. PDL1=Programmed death-ligand 1. PD1=Programmed cell death 1. *Patients that performed re-challenge without experiencing disease progression after the first ICPi received as upfront treatment.			

**Table C: Univariate and multivariate analysis regarding progression-free survival at re-challenge**

Factor	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
<b>Discontinuation reason</b>		2·10 <sup>-2</sup>		
Disease progression	1			
Toxicity	0·54 (0·33–0·86)			
Clinical decision	0·63 (0·37-1·07)			
<b>Chemotherapy between the two ICP rounds</b>		4·10 <sup>-3</sup>		
No	1			
Yes	1·81 (1·21-2·72)			
<b>ECOG-PS at re-challenge</b>		6·10 <sup>-3</sup>		<b>6·10<sup>-3</sup></b>
ECOG PS 0	1		1	
ECOG PS 1	2·12 (1·25-3·60)		2·12 (1·25-3·60)	
ECOG PS 2-3	2·74 (1·42-5·26)		2·74 (1·42-5·26)	
<b>Treatment line at re-challenge</b>		9·10 <sup>-2</sup>		
First or second line	1			
Third line	1·17 (0·61-2·27)			
Further lines	1·74 (0·97-3·14)			
<b>Bone MTS</b>		1·10 <sup>-1</sup>		
No	1			
Yes	0·67 (0·41-1·09)			
<b>Brain MTS</b>		1·10 <sup>-1</sup>		
No	1			
Yes	1·46 (0·92-2·31)			
<b>N° of MTS sites</b>		2·10 <sup>-1</sup>		
0 MTS	1			
1 MTS	0·79 (0·48-1·29)			
≥2 MTS	1·27 (0·78-2·06)			

Only statistically significant factors with an  $\alpha$  error  $\leq 20\%$  at the Cox univariate model and with an  $\alpha$  error  $< 5\%$  at the Cox multivariate analysis were reported.  
PS=performance status. MTS=metastasis. HR=hazard ratio.



**Table D: Univariate and multivariate analysis regarding overall survival from re-challenge**

Factor	Univariate analysis		Multivariate analysis	
	HR (95%CI)	<i>P</i> value	HR (95%CI)	<i>P</i> value
<b>Discontinuation reason</b>		$3 \cdot 10^{-2}$		
Disease progression	1			
Toxicity	0.44 (0.23-0.82)			
Clinical decision	0.61 (0.23-0.82)			
<b>Chemotherapy between the two ICPI rounds</b>		$1 \cdot 10^{-1}$		
No	1			
Yes	1.52 (0.90-2.60)			
<b>ECOG-PS at re-challenge</b>		$1 \cdot 10^{-2}$		$1 \cdot 10^{-2}$
ECOG PS 0	1		1	
ECOG PS 1	2.98 (1.32-6.75)		2.98 (1.32-6.75)	
ECOG PS 2-3	3.97 (1.60-9.87)		3.97 (1.60-9.87)	
Only statistically significant factors with an $\alpha$ error $\leq 20\%$ at the Cox univariate model and with an $\alpha$ error $< 5\%$ at the Cox multivariate analysis were reported. ICPI=immune checkpoint inhibitor. PS=performance status. HR=hazard ratio.				

**Supplementary Table A: Grade  $\geq$  III toxicities during the first ICPis round and at re-challenge.**

<b>Discontinuation reason</b>	<b>Grade <math>\geq</math>3 toxicity during the first ICPis</b>	<b>Grade <math>\geq</math>3 toxicity during re-challenge</b>
Toxicity	Skin toxicity	Arthralgia
Toxicity	Skin toxicity	Nephritis
Toxicity	Skin toxicity	No
Toxicity	Skin toxicity	No
Toxicity	Skin toxicity	No
Toxicity	Skin toxicity	No
Toxicity	Pneumopathy	Pneumopathy
Toxicity	Pneumopathy	Pneumopathy
Toxicity	Pneumopathy	No
Toxicity	Pneumopathy	No
Toxicity	Pneumopathy	No
Toxicity	Colitis	No
Toxicity	Colitis	No
Toxicity	Colitis	No
Toxicity	Colitis	No
Toxicity	Hypophysitis	No
Toxicity	Hypophysitis	No
Toxicity	Arthralgia	No
Toxicity	Arthralgia	No
Toxicity	Hepatitis	No
Toxicity	Diarrhea	No
Toxicity	Hyperglycemia	No
Toxicity	Peritonitis	No
Toxicity	Hematological toxicity	No
Toxicity	Nephritis and thyroiditis	No
Toxicity	Hepatitis and thyroiditis	No
Toxicity	Not specified	No
Disease progression	No	Not specified
Disease progression	No	Pneumopathy
Disease progression	No	Not specified
Clinical decision	No	Pneumopathy
Clinical decision	No	Colitis

## Figure legends

### **Figure A: Schematic disease history of the study cohort**

CT=chemotherapy. ICPI=immune checkpoint inhibitor.

### **Figure B: Best response upon first anti-PD1/PDL1 round and re-challenge**

NA=not available. PD=progressive disease. SD=stable disease. PR=partial response. CR=complete response. anti-PD1=anti-programmed cell death-1. anti-PDL1=anti-programmed cell death ligand-1.

### **Figure S1: Progression-free survival upon first ICPI round and re-challenge**

ICPI=immune checkpoint inhibitor.

### **Figure S2: Overall survival from the first ICPI (OS1) round and re-challenge (OSR)**

ICPI=immune checkpoint inhibitor. OS1=overall survival upon first ICP1. OSR=overall survival upon ICP1 re-challenge.

### **Figure S3: Swimmer plot of overall survival upon first ICPI round in the whole study population**

ICPI=immune checkpoint inhibitor.

**N = 144**  
WHOLE COHORT

First ICPI discontinuation reason

**N = 58**  
DISEASE PROGRESSION

**N = 58**  
TOXICITY

**N = 28**  
CLINICAL DECISION

CT between the  
two ICPI rounds

**N = 48**  
YES

**N = 10**  
NO

CT between the  
two ICPI rounds

**N = 12**  
YES

**N = 46**  
NO

CT between the  
two ICPI rounds

**N = 2**  
YES

**N = 26**  
NO

## Best response %(n)

