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Reviewer A

Comment 1: The sample size is rather low. In addition, this is a single-institution retrospective study. Validation of the results using an independent cohort would significantly improve the manuscript.
Reply 1: Thank you very much for your suggestion. Regrettably, this report is a preliminary and retrospective study. We will try to set up a prospective study for validation of the relationship between tumor growth rate and ICIs' efficacy in future because we evaluated the relationship retrospectively by use of linear and non-linear correlation analysis in this paper.
Changes in text: We added the underlined phrase in line 283 - 284 in *Discussion*: "First, this investigation was a small-scale retrospective study at a designated regional cancer treatment hospital in Japan; therefore, we will set up an independent cohort to validate the results."

Comment 2: Some analysis such as the correlation between IRP and PDL1 staining or TMB would be of particular interest.
Reply 2: We also examined the correlation between IRP and PD-L1 expression, and drew new Figure 3b; however, IRP and PD-L1 expression showed no correlation. Because TMB was not measured at our facility, we could not examine the relationship between IRP and TMB.
Changes in text: we added the following sentence in lines 214 - 216 in *Results*, "IRP and PD-L1 expression were also not correlated in 39 patients, in which PD-L1 expression had been measured; MIC, 0.234; and Spearman's rank correlation coefficient, 0.111 (p = 0.502) (Fig 3b)." We made new Figure 3b, and added a figure legend for Figure 3b in lines 391 - 394: "**b** Scatter plot showing correlation between initial rapidity of tumor progression and expression of programmed death-ligand 1. They revealed no correlation. *MIC* maximal information coefficient, *Spearman* Spearman's rank correlation coefficient"

Comment 3: Was IRP significantly associated with tumour response to treatment at 3- 6- or 9. months? A box plot showing IRP values on patients showing a complete response, partial response stable disease, and progression disease at a given time would facilitate understanding the potential value of this biomarker.
Reply 3: We evaluated the response at 3, 6, and 9 months after ICI administration, and drew box plots of IRP grouped with response to ICI. Patients with PD response at nine months after ICI administration had shown significant initial-rapid progression.
Changes in text: We made new Figure 4 to show the relationship between IRP and the response to

treatment at 3, 6, and 9 months after ICI administration. We added the following underlined abbreviations for indication of response to treatment in lines 165 - 167 in *Results*; "The best confirmed response to ICIs was: complete response (CR), 5 (9.1%); partial response (PR), 14 (25.5%); stable disease (SD), 27 (49.1%); and progressive disease (PD), 9 (16.4%)."

We added the following paragraph in lines 217 - 232 in *Results*: "The relationship between IRP and the response to treatment after 3, 6, and 9 months after ICI administration was evaluated (Fig. 4). The median IRP in each response to treatment were the followings: CR, (n = 3), 0.18 mm/days (range 0.02 - 0.20 mm/days); PR (n = 16), 0.13 mm/days (0.03 – 1.17 mm/days); SD (n = 18), 0.085 mm/days (0.02 - 0.45 mm/days); and discontinuation of ICI (n = 15), 0.3 mm/days (0.09 - 2.09 mm/days) at three months after ICI administration ($p = 0.0217$); CR (n = 2), 0.11 mm/days (0.04 – 0.18 mm/days), PR (n = 9), 0.32 mm/days (0.02 – 1.17 mm/days); SD (n = 9), 0.08 mm/days (0.02 – 0.45 mm/days); PD (n = 3), 0.09 mm/days (0.02 – 0.20 mm/days); and discontinuation of ICI (n = 31), 0.22 mm/days (0.03 – 2.09 mm/days) at six months ($p = 0.24$); and CR (n = 3), 0.04 mm/days (0.02 – 0.18 mm/days); PR (n = 5), 0.13 mm/days (0.05 – 0.39 mm/days); SD (n = 5), 0.06 mm/days (0.02 – 0.12 mm/days); PD (n = 4), 0.565 mm/days (0.33 – 1.17 mm/days); and discontinuation of ICI (n = 36), 0.2 mm/days (0.02 – 2.09 mm/days) after nine months ($p = 0.00834$). Due to lack of appropriate examination, 3, 1, and 2 patients were excluded from the evaluation at 3, 6, and 9 months, respectively."

We added a legend for Figure 4 in lines 396 - 399 in *Figure legends*: "**Fig. 4** Box plots showing initial rapidity of tumor progression in each response to immune-checkpoint inhibitors (ICI) at 3 (**a**), 6 (**b**), and 9 (**c**) months after ICI treatment. *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progression disease".

Comment 4: Table 1 shows clinicopathological features according to the line of treatment. In my opinion median and range of IRP according to clinicopathological features should be presented. Was IRP associated with any of these features?

Reply 4: We examined IRP in each clinicopathological features, and evaluated the relationship with non-parametric multiple test. The *p* value was 0.393; therefore, IRP was not significantly associated with difference in clinicopathological features. This result is shown in Figure 3a.

Changes in text: We added the following sentence for comparison between multiple groups in *Statistics* in lines 141 - 142 in *Methods*: "Three or more groups were compared with a non-parametric multiple test, Kruskal-Wallis test."

We also added the following sentences in lines 208 - 214 in *Results*: "IRP was evaluated according to histology of lung cancer or PD-L1 expression. Median IRP in each histology of lung cancer is the followings: 0.125 mm/days (range 0.02 - 0.93) in adenocarcinoma, 0.115 mm/days (0.04 - 1.17) in NSCLC, which was impossible to be determined as detailed types, 0.270 mm/days (0.03 - 2.09) in squamous cell carcinoma, and 0.15 mm/days and 0.09 mm/days in the other two types ($p = 0.393$) (Fig 3a); therefore, IRP was not associated with histology of lung cancer.", and a figure legend in lines 390

- 391 in *Figure legends*, "**Fig. 3 a** Box plot showing initial rapidity of tumor progression in each histology of lung cancer."

Comment 5: A thorough description on how summed diameters are calculated should be provided? Were these analyses performed by a single investigator?
Reply 5: Measurable tumor lesions were defined according to the RECIST guideline version 1.1, and measured by a specialized physician in respiratory diseases and a data management assistant who are listed as the first and second author. We clarified these points in *Methods*.
Changes in text: We added sentences in lines 122 - 128 in *Procedures* of *Methods*: "After intrathoracic tumor lesions were detected, lung lesions of 10 mm or more in a major axis and lymph nodes of 15 mm or more in a minor axis were defined as measurable lesions, and the top two largest lesions in each lung and lymph nodes were measured for IRP calculation. For response evaluation, up to 5 lesions including other organ lesions were measured. A specialized physician in respiratory diseases and a data management assistant measured lesions according to the RECIST guideline version 1.1."

Comment 6: Some data that is missing is of particular interest as for example range of TTF (days), median, and range of days between initial check-up and the start of treatment.
Reply 6: We added range of TTF, and median and range of the days between the first CT scan at initial checkup and the second CT scan just before the first treatment.
Changes in text: We added the underlined parts in lines 172 - 173 and in lines 175 - 176 in *Results*: **"**The median TTF of ICI treatment for all 55 patients was 126 days (range 64 - 1311 days) (Fig. 1b)", and "with the median TTF, 225 days (38 - 1311 days) and 121 days (28 - 925 days), respectively (Fig. 1c)."

We added sentences in lines 177 - 179: "The median interval between the first CT scan at initial checkup and the second CT scan just before treatment was 44 days (range 5 - 1573 days), and median IRP during the period was 0.14 mm/days (0.02 - 2.09 mm/days)."

Reviewer B

Comment 1: - You imply in your introduction that PD-L1 TPS status is not a predictor of ICI efficacy. This contradicts well established research, which you in fact refer to throughout your introduction. For example, Keynote-189 demonstrated that patients with PD-L1 TPS >50% treated with ICI combination had a HR of 0.36 for disease progression or death, compared to placebo; while TPS 1-49% had a HR of 0.55 and <1% was 0.75. These findings are also reflected in other major RCTs (eg Keynote-042).
- You could omit some of your opening lines which are not necessary.

Reply 1: Thank you very much for your suggestion. We intended to describe purpose for search of other predictors for ICIs' efficacy than PD-L1 expression; however, our description was misleading. We deleted "which contradicts the notion that PD-L1 is a predictor of ICI efficacy".

Changes in text: We deleted "which contradicts the notion that PD-L1 is a predictor of ICI efficacy" after "However, at present, ICIs in combination with cytotoxic chemotherapies have been approved as the first-line treatment for lung cancer regardless of PD-L1 expression" in lines 78 - 80 in *Introduction*,

Comment 2: - I am confused as to why the Gompertz model of tumour growth kinetics influences your supposition that initial tumour growth rate relates to prognosis with ICI treatment. Please either clarify this or omit it.

Reply 2: We introduced the Gompertzian model to explain that tumor size is not always linearly correlated with tumor growth rate, and to suggest that tumor growth rate may be a more effective prognostic predictor than tumor size; However, it was confusable. In *Introduction*, we deleted the sentence which does not lead to our conclusion.

Changes in text: We changed the sentence in lines 91 - 93 in *Introduction*. We deleted "As the Gompertzian model indicates that growth rate non-linearly relates to tumor burden, and the growth rate may change stochastically in each tumor growth phase,", and add the following underlined clause: "We anticipated that tumor growth rate, which is in addition of time factor to tumor diameter, might relate to prognosis with ICI treatment."

In *References*, "14. Speer JF, Petrosky VE, Retsky MW, et al. A stochastic numerical model of breast cancer growth that simulates clinical data. Cancer Res 1984; 44: 4124-30." was deleted.

Comment 3: - ITS was defined as the sum of diameters of intrathoracic tumours and lymph nodes. Were there any cases of bulky extrathoracic metastases which were not considered in your calculations, and thus may confound your final results? Please clarify.

Reply 3: We reviewed the patients with extrathoracic metastasis at first, and summarized them. We described the treatment for a metastatic lesion with, particularly bulky mass.

Changes in text: We added the following sentences in lines 179 - 191 in *Results*: "Twenty-five patients had extrathoracic metastases before the first treatment, and the median sum of diameters in each metastatic site was the followings: the brain (n = 10), 18.75 mm (range 3.7 – 38.4 mm); the bone (n = 12), 26.15 mm (3.5 – 86.0 mm); the liver (n = 2), 20.2 and 25.1 mm; the adrenal gland (n = 4), 20.15 mm (17.4 – 39.4 mm); the extrathoracic lymph node (n = 2), 10.2 mm and 34.3 mm; and the muscle (n = 1), 8.4 mm. A patient with a 38.4-mm nodule in cerebellum underwent tumor resection before ICI administration, and recurrence did not occur in the brain during the second-line pembrolizumab treatment. A patient with an 86-mm bulky mass in the ilium underwent radiation therapy, which apparently shrunk the bone mass, leading to osteosclerosis without fluorodeoxyglucose accumulation.

While the patient received nivolumab treatment, recurrence did not occur in the bone."

Comment 4: - Furthermore, although I acknowledge that conventional radiology interpretation of tumour size is to use 2-dimensional measurements (eg. RECIST) to assess tumour burden and response to treatment, perhaps automated 3D volumetric analysis (becoming more commonly employed in lung nodule analysis) would improve sensitivity and reliability of your findings. Is it possible to repeat your study using 3D volumetric analysis instead?

Reply 4: Thank you very much for your suggestion. In this research, we searched a handy method for a prognostic predictor, and unfortunately, the application program for calculation of 3D volume is not available in most CT scans. We would like to apply 3D-volume measurement to IRP calculation in future. We added this point as a limitation in *Discussion*.

Changes in text: We added the following sentences in lines 288 - 290 in *Discussion*: "Thirdly, tumor size and response to ICIs were measured on two-dimensional CT scans according to the RECIST guideline. Three-dimensional measurement may improve accuracy of the results."

Comment 5: - I note that this was a small sample size, and that 40% of patients were treated with the first-generation ICI, nivolumab. This limits the external validity of your findings and should be noted.

Reply 5: We described as a limitation that our results may be affected by nivolumab treatment.

Changes in text: We added the following sentence in lines 291 - 292 in *Discussion*: "Fourthly, 40% of patients received nivolumab; therefore, our results may be affected by the first-released ICI."

Comment 6: - "TTF" was defined as time to withdrawal of ICI, however only 62% of patients had ICI withdrawn as a result of tumour progression. For example, 27% had ICI withdrawn due to irAE and therefore this is not "treatment failure", per se, but "treatment intolerance". A further 7.3% continued therapy past your follow-up period. This is a major flaw in your analysis and severely limits the generalisability/applicability of your results. You need to revise your findings, including only those who had ICI withdrawn due to tumour progression.

Reply 6: We performed the correlation analysis in only patients who were discontinued ICIs due to tumor progression, excluding patients with discontinuation of ICIs due to adverse events or ongoing ICI treatment. It did not show a significant correlation. We think that disappearance of significant correlation might be attributed to omission of patients who were able to have benefit by ICI treatment for TTF. We described it in the manuscript as the follows.

Changes in text: We made new Figure 6 using only patients with discontinuation of ICIs due to disease progression. We added the paragraph in lines 241 - 247 in *Results*: "Excluding patients with discontinuation of ICIs due to adverse events or ongoing ICI treatment, the correlation between TTF

and IRP, initial NLR or initial CRP-albumin ratio was not significant in only patients with discontinuation due to tumor progression (Fig. 6). Because some patients with discontinuation of ICI due to adverse events have longer TTF, excluding these patients in addition to patients with ongoing ICI treatment might omit patients who were able to have benefit by ICI treatment for TTF.", and added a figure legend for Figure 6 in lines 407 - 413: "Fig. 6 Scatter plots showing correlation between time to treatment failure (TTF) and initial rapidity of tumor progression (**a**), initial tumor size (**b**), initial neutrophil-lymphocyte ratio (**c**), and initial CRP-albumin ratio (**d**) in only patients with discontinuation of immune-checkpoint inhibitor (ICI) due to tumor progression, excluding patients with discontinuation of ICI due to adverse events or ongoing ICI treatment. *MIC* maximal information coefficient, *Spearman* Spearman's rank correlation coefficient, *CRP* C-reactive protein"

Comment 7: - Your results suggest that initial tumour size stability, or low IRP, prior to therapy leads to a longer time to treatment failure (TTF). Is this a characteristic of the tumour properties rather than their response to treatment? In other words, did the treatment influence their medium-term disease stability? Perhaps not.

Reply 7: It is very difficult to determine which is beneficial for TTF, ICI treatment or inherent characteristics of tumor. Lower level of IRP as inherent characteristics in tumor might lead to longer overall survival time; therefore, we adopted TTF as an endpoint for evaluation of ICI efficacy, because we expected that TTF, treatment duration of ICI, was less susceptible to inherent growth rapidity of tumor, which could be suppressed while ICI was effective.

Changes in text: We changed the sentence at discussion in lines 299 - 300 in *Discussion*: from "This result suggests that the effect of ICIs is less beneficial in acutely progressive tumors." to "This result suggests that the effect of ICIs is less beneficial in tumors with acutely progressive in their inherent characteristics."