Serum Alanine Aminotransferase As An Early Marker of Outcomes in Patients Receiving Immuno-Oncology Drugs

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Research Article

Keywords: Immunotherapy, Immuno-onlogy drug, Nivolumab, Pembrolizumab, Iplimumab, Advanced cancer, Response predictive factor

Posted Date: February 2nd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-155568/v1

Abstract

Immune-oncology (IO) drug therapy is effective against various types of cancer. Although several, potential, clinical, predictive markers have been identified, none so far have proven reliable. Herein we evaluated changes in serum alanine aminotransferase (ALT), which is upregulated by the accumulation of activated CD8 + T cells in the liver, as a potentially reliable predictive marker. We retrospectively analyzed 265 patients with advanced malignancies at three institutions between 2016 and 2019. The patients received IO drug therapy. We defined the ALT ratio (ALR) as the serum ALT value at baseline / the highest serum ALT during IO drug therapy, then determined whether the ALR correlated with the objective response rate or progression-free survival. The median follow-up was 3.1 months. We observed objective responses in 65 patients. The ALR ranged from 0.19 to 32.2 (median 1.5), and a significant ALR increase was observed in responders ($p < 0.001$). In receiver operating characteristic analysis, ALR = 1.55 had the highest sensitivity and specificity. The patients with ALR < 1.55 had a significantly poorer PFS than those with ALR ≥ 1.55. A high ALR was associated with a tumor response and good PFS in patients with advanced malignancies. The ALR is a reliable predictive marker based on activated cytotoxic T lymphocyte dynamics.

Introduction

Programmed death-1 (PD-1) is inducibly expressed by activated cytotoxic T lymphocytes (CTLs). PD-1 interacts with its ligand, B7-H1, to deliver an inhibitory signal to CTLs [1,2]. Cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) is also inducibly expressed on CTLs and interacts with its ligand, CD80 or CD86, to deliver an inhibitory signal to CTLs [3,4]. Both molecules inhibit antitumor immunity. Anti-PD-1 and anti-CTLA-4 antibody block the inhibitory signal, thereby activating the CTLs against the cancer [5–8]. Recently, anti-PD-1 and anti-CTLA-4 antibodies were approved for use against several cancers [9,10]. These antibodies are comprehensively referred to as immune-oncology (IO) drugs. Nivolumab was effective against non-small-cell lung cancer (NSCLC) [11,12], melanoma [13], renal cell carcinoma (RCC) [14], urothelial carcinoma (UC) [15,16], squamous cell carcinoma of the head and neck (SCCHN) [17], gastric cancer (GC) [18], malignant mesothelioma (MM) [19], Hodgkin's lymphoma [20], and hepatocellular carcinoma [21]. Pembrolizumab, another anti-PD-1 antibody, was also effective against NSCLC [22], melanoma [23], RCC [24], SCCHN [25], UC [26], and Merkel cell carcinoma [27]. Iplimumab was effective against melanoma [10] and RCC [28].

Despite their efficacy, IO drugs benefit only a small number of patients. Therefore, reliable predictive markers allowing the identification of responders and non-responders is crucial to choosing the optimal treatment. Several studies have discussed predictive markers, such as PD-L1 expression [29], overall mutational burden [30], leukocyte count [31–33], lactate dehydrogenase [33,34], C-reactive protein [35] and adverse events [36–38], but as yet, no reliable predictive marker has been found.

CTLs, which are activated by IO drugs, accumulate in the liver and undergo apoptosis [39,40]. Dong et al. showed a greater accumulation of CTLs in the liver of B7-H1- deficient mice than in wild-type mice [41]. In the present study, we evaluated changes in the serum alanine aminotransferase (ALT) level, which is a marker of liver injury, as a mechanism-based predictive marker for IO drug therapy.

Results

Patient characteristics

In total, 265 patients (134 with NSCLC (92 with adenocarcinoma and 42 with SCC); 38 with GC; 52 with RCC; 35 with UC; three with MM; and three with an unknown primary cancer) were enrolled (**Table 1**). The median follow-up period was 3.1 months (0.2-46.3). The average age was 69.3 years (42-88), and the male: female ratio was 193 : 72. We observed objective responses in 65 patients (44 with NSCLC (26 with adenocarcinoma and 18 with SCC); four with GC, ten with RCC; five with UC; one with MM; and one with an unknown primary cancer).

ALR according to the response to immunotherapy

The ALR ranged from 0.19 to 32.2 (median 1.5). We observed a significant increase in the ALR among responders ($p<0.001$, **Figure 1**). The ALR was able to predict the tumor response, as determined by ROC curve sensitivity (0.85) and specificity (0.70) **(Figure 2**). We observed an increase in the ALR (≥1.55) in 54 of 65 responders (42 of 55 patients with a PR and 10 of 10 patients with a CR) and 67 of 200 non-responders (27 of 55 patients with SD and 40 of 145 patients with PD) (odds ratio:9.7, $p<0.0001$, **Figure 3**). In 67 non-responders with an elevated ALR, 12 experienced exacerbation or liver metastasis, nine experienced adverse events associated with immunotherapy (liver toxicity, etc.), and ten showed a mixed response, in which some tumors shrank, but PR was not achieved or a new metastasis occurred.

Timing of the serum ALT increase in responders

We analyzed the timing of the serum ALT increase in 52 responders (**Figure 4A**). The serum ALT increased in 28 (54%) and 42 (81%) patients within 30 and 60 days, respectively, following the initial drug infusion. In all the responders, a serum ALT increase occurred within three months. Next, we evaluated the differences by drug. In patients receiving nivolumab, one (4%), 11 (40%), and 21 (75%) of 28 patients showed a serum ALT increase within 10, 30, and 60 days, respectively, following the initial drug infusion. In patients receiving pembrolizumab, eight (35%), 17 (71%), and 23 (100 %) of 23 patients showed a serum ALT increase within 10, 30, and 60 days, respectively, following the initial drug infusion. Variations in the timing of the response after the serum ALT increase were also analyzed (**Figure 4B**). In fourteen (27%), 37 (71%), and 44 (85%) of 52 patients, the response developed within 30, 60, and 90 days, respectively, following the serum ALT increase. In patients receiving nivolumab, one (4%), 11 (40%), and 21 (75%) of 28 patients developed the response within 10, 30, and 60 days, respectively, following the initial drug infusion. In patients receiving pembrolizumab, eight (35%), 17 (71%), and 23 (100 %) of 23

patients developed the response within 10, 30, and 60 days, respectively, following the initial drug infusion.

Progression-free survival estimated using the ALR

Among patients with NSCLC, GC, RCC, and UC, an ALR<1.55 was associated with significantly poorer PFS than ALR≥1.55. The median PFS among patients with NSCLC with ALR<1.55 and ALR≥1.55 was 2.6 and 12 months, respectively (p<0.001, **Figure 5A**). Subgroup analysis performed for tumor histology demonstrated that elevated ALR remained a significant prognostic factor. The median PFS in patients with adenocarcinoma with an ALR<1.55 and ALR≥1.55 was 2.9 and 11.2 months, respectively (p=0.002, **Figure 5B**). The median PFS in patients with squamous cell carcinoma with an ALR<1.55 and ALR≥1.55 was 1.5 and 20.3 months, respectively (p<0.001, **Figure 5C**). Elevated ALR was a significant prognostic factor in patients with gastric cancer, RCC, and UC. The median PFS in patients with gastric cancer with an ALR<1.55 and ALR≥1.55 was 1.8 and 2.2 months, respectively (p=0.015, **Figure 5D**). The median PFS in patients with RCC with an ALR<1.55 and ALR≥1.55 was 4.1 months and not achieved, respectively (p=0.006, **Figure 5E**). The median PFS in patients with UC with an ALR<1.55 and ALR≥1.55 was 1.4 and 6.5 months, respectively (p<0.001, **Figure 5F**).

Discussion

Crispe et al. revealed that CTLs activated by an antigen were deleted in the liver, suggesting either a preferential accumulation in the liver of activated CTLs undergoing apoptosis (the graveyard hypothesis) or a trap for activated CTLs in the liver for subsequent killing (the killing field hypothesis) [39,40]. In B7-H1 deficient mice, activated PD-1 + CD8 T cells accumulated in the liver [41]. We surmised that the accumulation and deletion of activated CTLs in the liver might impose a burden on the liver, which could induce hepatopathy and elevate serum liver enzymes [42]. After assessing both serum aspartate aminotransferase and ALT, we found that serum ALT was a better predictive marker (data not shown).

The timing of the serum ALT increase varies for each IO drug. In most patients receiving pembrolizumab or a combination of nivolumab and ipilimumab, the timing of serum ALT elevation was one to three weeks following the initial drug infusion. However, the timing for nivolumab was different, varying from soon after the initial infusion to later in some cases. This difference may depend on the affinity of each IO drug to the PD-1 molecule. An antibody with a strong affinity might affect the immune system sooner than an antibody with a weaker affinity; pembrolizumab has stronger affinity to the immune system than nivolumab. Usually, serum ALT rises immediately prior to the finding of tumor shrinkage on a radiologic modality. These findings suggested that ALR might serve as a predictive marker of IO drug therapy.

The present study has the limitations inherent in any retrospective analysis. The patient population varied widely. The ALR was not a perfect predictive marker and presented certain some problems, such as the occurrence of false negative and false positive cases. We observed no increase in the ALR in 11 (17.0 %) responders while we found an increase in 67 (33.5 %) non-responders. There are a number of possible

explanations for the false negatives. First, our timing of ALT analysis was inadequate in that we failed to perform the analysis when the ALT had reached its highest value. Second, because injury to the liver was small, we did not observe elevations in the serum ALT levels. There are two reasons for the low level of injury to the liver. First, the shrunken tumor volume was too small to induce sufficient CTL activation to cause hepatopathy; in effect, there was insufficient injury to the liver to elevate the ALT level. Another reason for the minimal injury to the liver was very good liver function.

There are also a number of possible explanations for the false positive results. In twelve patients, a new liver metastasis or the progression of an existing liver metastasis induced a serum ALT increase. In nine patients, other reasons, for example, autoimmune hepatitis, autoimmune cholangitis, septic shock, other drug-induced hepatopathy, etc., accounted for the elevated ALT. In ten patients, despite the achievement of SD or PD according to the RECIST criteria, a portion of the tumors showed shrinkage. We were able to identify other, clinical causes of elevated ALT as well; after excluding 21 cases of elevated ALT due to other causes from the cohort and adding ten cases showing some tumor shrinkage to the responder group, the odds ratio rose from 9.7 to 16.8. In clinical practice, the ALR may serve as a very promising predictor of the response to IO drug therapy when transitioning to the next treatment.

The PFS duration was significantly longer in the high ALR group than in the low ALR group for four types of cancer, suggesting that the ALR can help differentiate between long and short SD among non-responders. The ALR is useful for patients receiving cancer immunotherapy because it facilitates judging whether immunotherapy should be continued or switched to an alternative treatment. Previous studies have reported several, reliable predictive markers for IO drug therapy, including PD-L1 expression and tumor mutation burden [43]. However, these factors have limitations due to cost-related concerns; these markers require additional analysis, the involvement of specialists or the use of expensive equipment. In contrast to those markers, some studies revealed that certain blood and clinical markers can be routinely used, such as the leukocyte count, lactate dehydrogenase, and adverse events [43]. ALR is also one such available blood markers. However, in this respect the ALR, based on CTL dynamics, is a superior marker of immunotherapy and has the potential to serve as a simple, reliable prognostic marker in risk stratification and provide better treatment allocation in cancer patients.

A high ALR was associated with the tumor response and PFS in patients with various types of cancer. An increase in ALT levels during IO drug therapy is reliable because it is based on activated CTL dynamics, making the ALR an useful predictive marker. Further studies aimed at refining the use of the ALR as a predictive marker based on the mechanism of IO drugs therapy are warranted.

Materials And Methods

Patients

Between 2016 and 2019, we reviewed the medical records of 265 patients with advanced malignancies at Tokyo Metropolitan Tama Medical Center, Kanto Rosai Hospital, and Tomishiro-Chuo Hospital, who

received single-agent nivolumab, pembrolizumab or a combination nivolumab and ipilimumab treatment. The study was approved by the ethical review board of Tama Medical Center, Kanto Rosai Hospital and Tomishiro Central Hospital as well as was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. Comprehensive informed consent was obtained from all participants.

Treatment and response assessment

Patients received nivolumab 3 mg/kg every two weeks, pembrolizumab 200 mg every three weeks or nivolumab 240 mg every three weeks plus ipilimumab 3 mg per kilogram every three weeks in four doses, followed by nivolumab 240 mg every two weeks.

All the patients underwent a blood test before starting IO drug therapy until the end of follow-up, which was performed at intervals of one to two weeks. We defined ALR as: the serum ALT value at baseline / the highest serum ALT during IO drug therapy.

Computed tomography or magnetic resonance imaging was performed at baseline and repeated at eight to 12 weeks intervals. The clinical tumor response during treatment was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 based on the patients' medical records. We defined a clinical benefit as a complete response (CR), partial response (PR) or stable disease (SD). We defined progression-free survival (PFS) as the time from immunotherapy initiation to the date of progression.

Statistics

We performed statistical analyses using the JMP® software package, with $p < 0.05$ indicating statistical significance. We compared continuous variables using the two-tailed unpaired Student's t-test. To predict the response to, and prognosis of, IO drug therapy, we determined the optimal cutoff value of the ALR based on the receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC). We constructed the distribution of the recurrence-free survival (RFS) rate using the Kaplan-Meier method.

Declarations

Author Contributions

TA designed the present study and critically revised the manuscript. TA, TT, YM, SN, TO, K.I. and M.T. performed data collection. TA analyzed the data. TA wrote the manuscript. TA, TT, YM, SN, TO, K.I. and M.T. revised the manuscript. All the authors read and approved the final manuscript.

Conflicts of Interest

All the authors state that they have no conflicts of interest.

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Tables

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

Figures

Figure 1

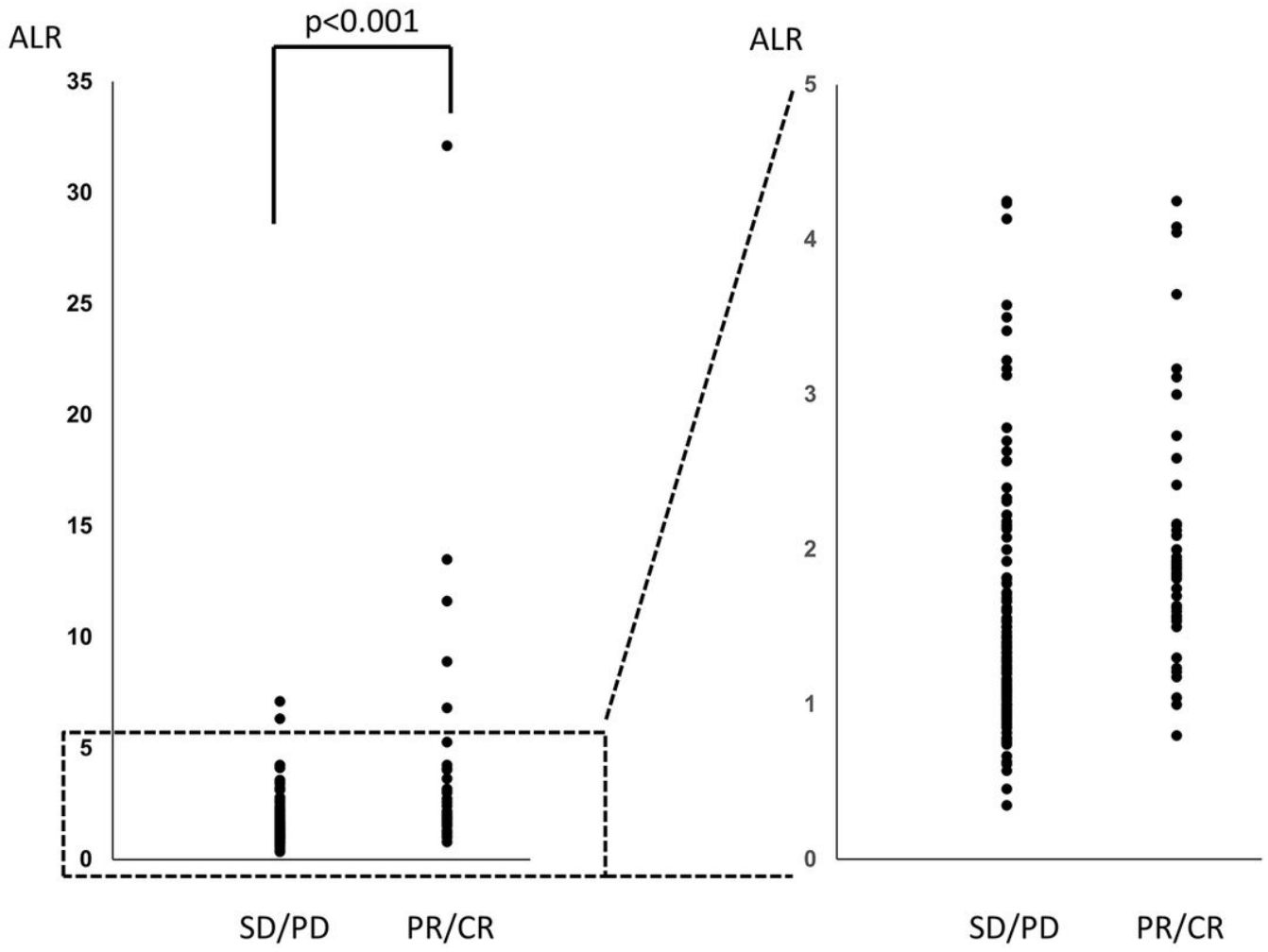

Figure 1

ALR according to the response to immunotherapy (SD/PD, stable/progressive disease; PR/CR, partial/complete response)

Figure 2

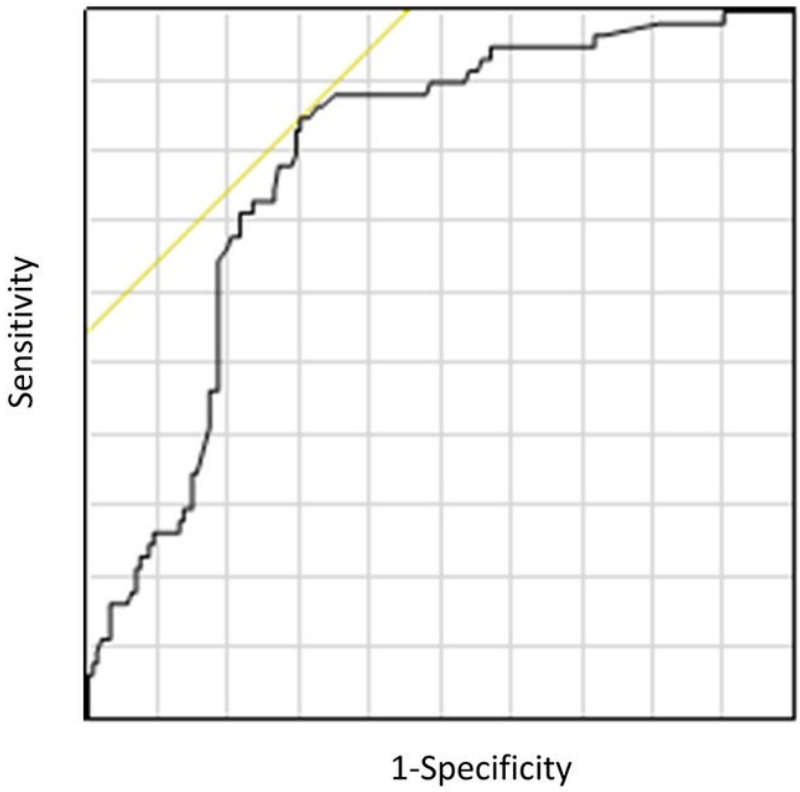

Figure 2

Receiver operating curve (ROC) analysis based on the ALR for the tumor response. In this model, the sensitivity was 85.0%, the specificity was 70.0%, and the AUC was 0.790. p<0.001. AUC, area under the curve.

Figure 3

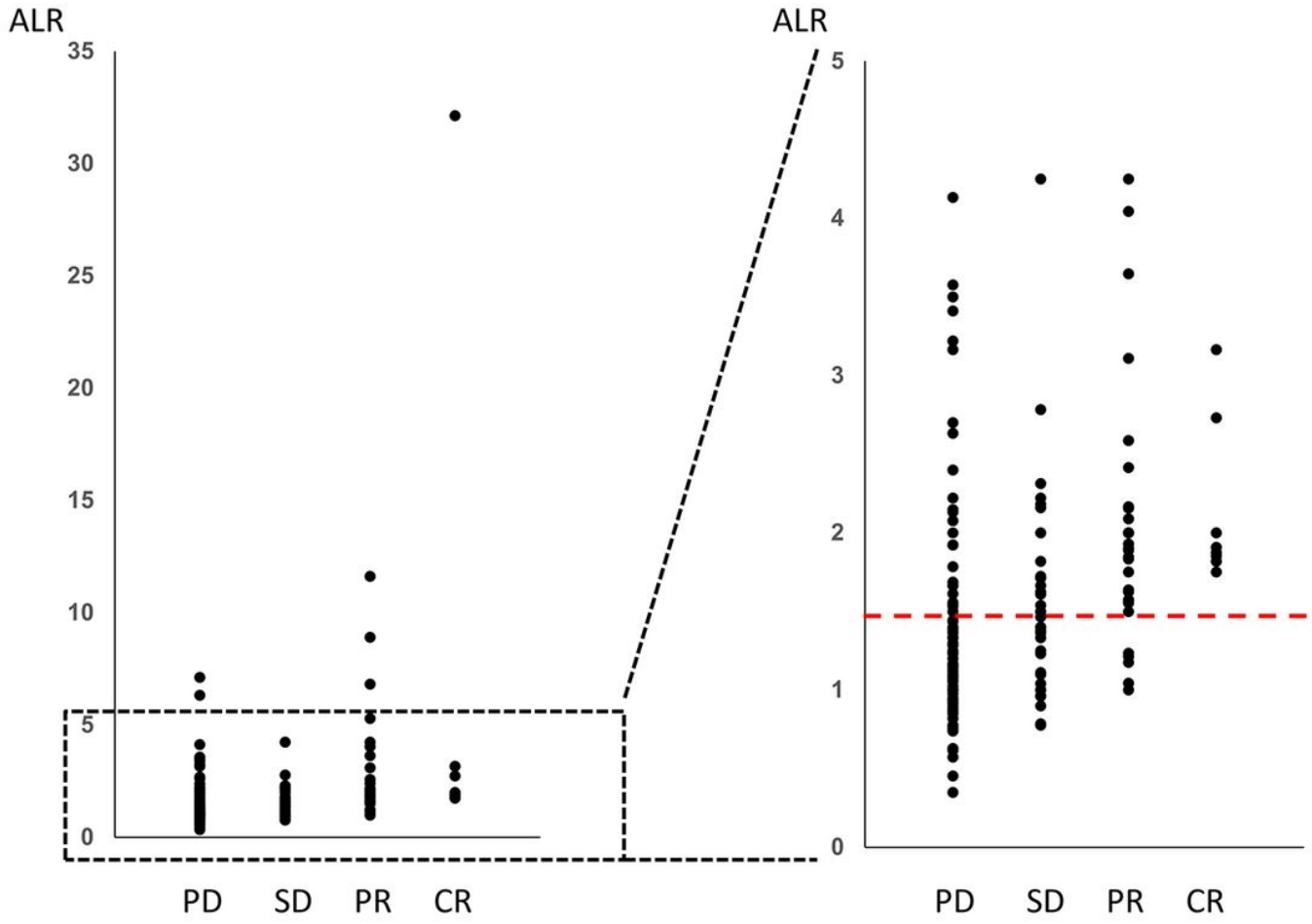

Figure 3

ALR according to the response to immunotherapy (CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease)

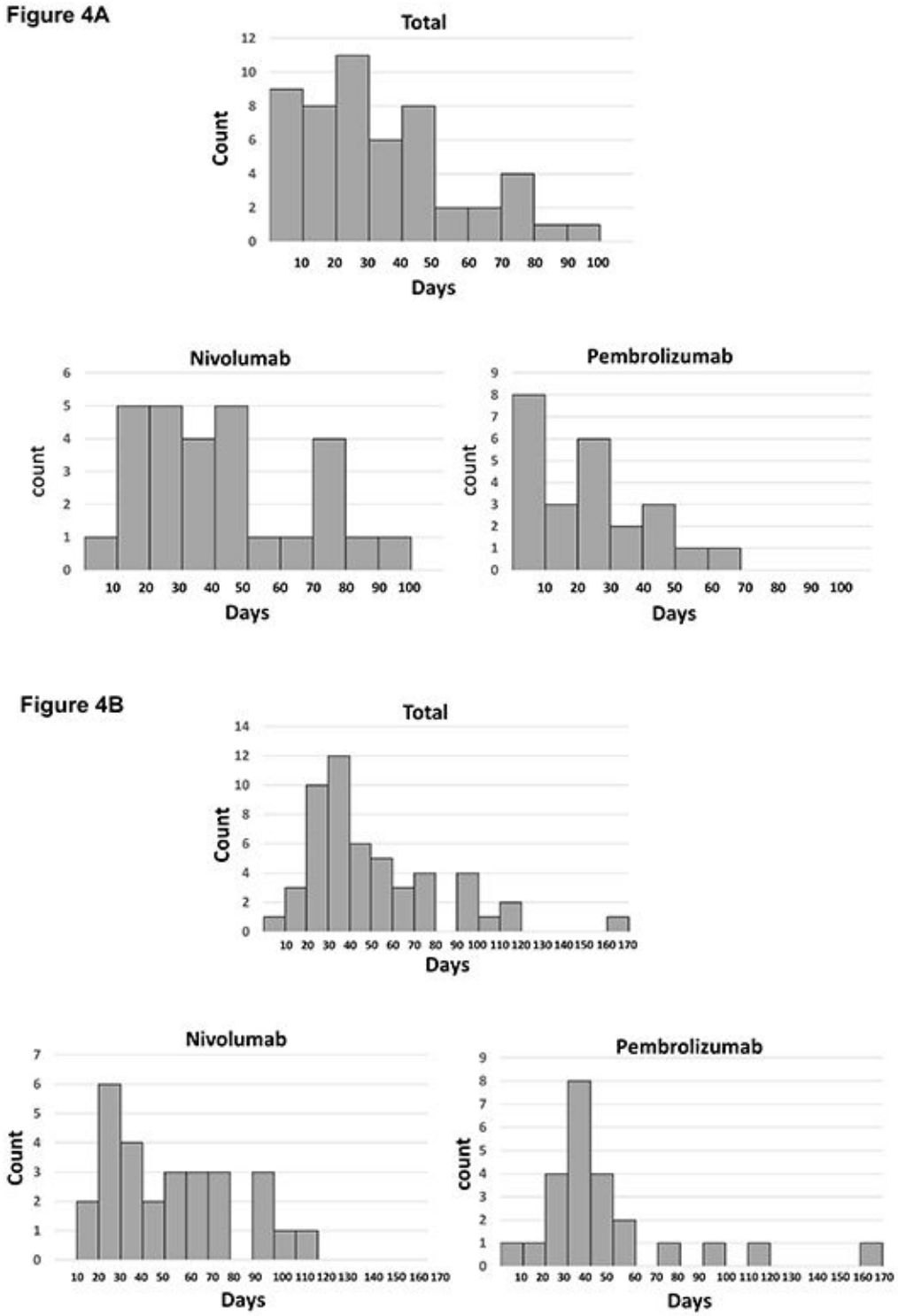

Figure 4

Timing of the serum ALT increase in responders.

Figure 5A

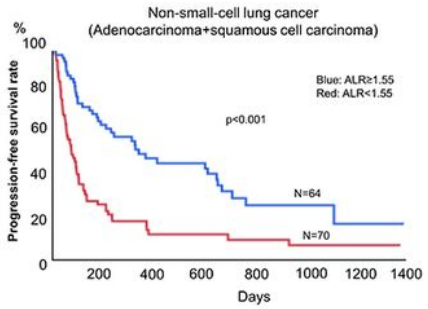

Figure 5B

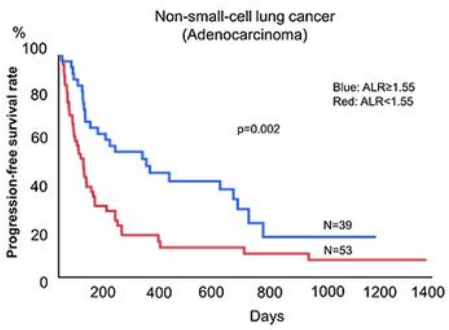

Figure 5C

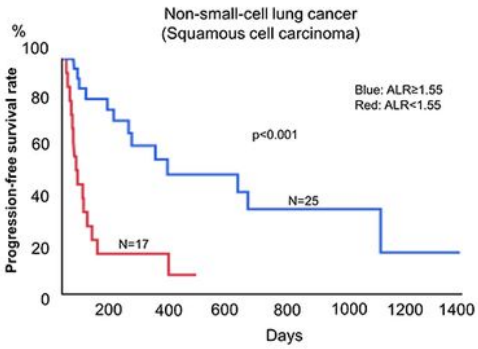

Figure 5D

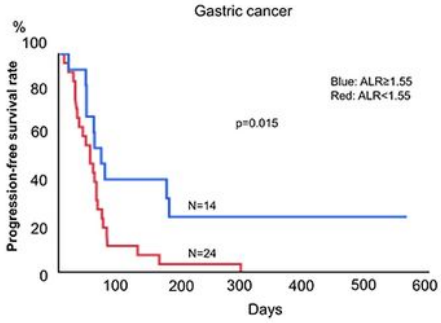

Figure 5E

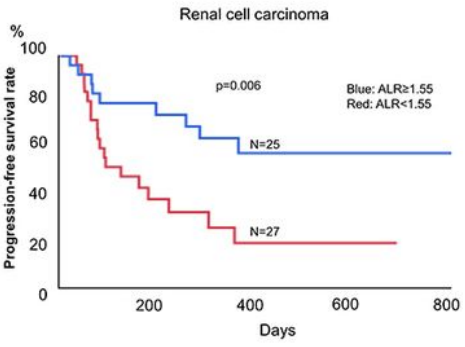

Figure 5F

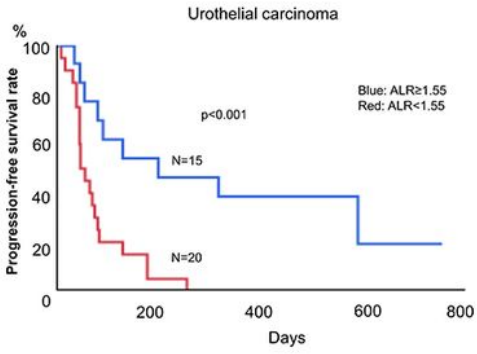

Figure 5

Progression-free survival (PFS) estimated using the ALR for non-small cell lung cancer (A), adenocarcinoma of the lung (B), squamous cell carcinoma of the lung (C), gastric cancer (D), renal cell carcinoma (E) and urothelial carcinoma (F).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.jpg