Peer Review File

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Reviewer A

Comment 1: In the baseline characteristics is missing the collection of autoimmune comorbidities at baseline of ICIs, and if there are active/on treatment or inactive. This should be added.

Reply 1: We are grateful to Reviewer A for his comment, as it allows us to offer clarification. Given that our study cohort exclusively consists of patients exposed to immune checkpoint inhibitors, and active autoimmune disease is a common contraindication to these therapies, we did not anticipate patients included in our study to have autoimmune comorbidities. Therefore, we opted not to collect this information in our Case Report Form (CRF).

Comment 2: The study enrolled patients who received Immunotherapy either as monotherapy or along with chemotherapy (row 90). The paper lacks a description of the role of chemotherapy. I recommend evaluating the impact of chemotherapy in terms of safety between SD and DD cohorts and in terms of efficacy. In my opinion, this represents a limitation of the study.

Reply 2: We thank reviewer A for his comment regarding the impact of chemotherapy in our study. In our cohort, only 7 patients had initial chemo-immunotherapy, whom 4 had adverse events during immunotherapy and none stopped the treatment because of toxicity. Those 7 patients had their first Double Dose of immunotherapy during the maintenance phase. Three of them stopped the Double Dose because of a progression respectively 4, 10 and 1 month after the switch. Therefore, it is safe to assume that it's not affecting our safety and efficacy conclusion. This has been clarified in the discussion section.

Changes in the text: Line 287-295 ". In our cohort, 7 patients underwent initial chemo-immunotherapy. Four experienced adverse events during immunotherapy (SD or DD). None discontinued treatment due to toxicity. All adverse effects were attributed to immunotherapy by the attending physician based on timing (after 4 cycles of chemotherapy) and type of AE (cytolysis, arthralgias, and pruritus). Concerning efficacy, these 7 patients received their first Double Dose of immunotherapy during maintenance. Three discontinued the double dose due to progression at 4, 10, and 1 month post-switch, respectively. Overall, the inclusion of patients initially treated with chemo-immunotherapy before the DD switch in our cohort is unlikely to affect our results."

Comment 3: The study enrolled patients (rows 89-91) who received at least

one dose of Pembrolizumab 400 mg or Nivolumab 480 mg. The authors did not mention about patients started Pembrolizumab 400 mg or Nivolumab 480 mg upfront and any shift to lower dosage (pembrolizumab 200 mg and nivolumab 240 mg)

Reply 3: This information is provided in the discussion section of the original manuscript. Line 229-230 : "Only 6 patients started upfront with DD regimen, 4 of them stopped very quickly because of progression disease." Among those who stopped DD regimen because of toxicity (n=19), 5 of them had to stop immunotherapy while the 14 others shift to standard dosage: Line 254-256 "Sixteen percent (19/117) of patients of our cohort underwent toxicity-induced extended regimen failure with 26 % of them (i.e 5/117) who had to definitely stop immunotherapy".

Comment 4: Specify, at row 89, the version of TNM stage classification used on the study. Moreover, indicate the subtype of stage III, on the text and in Table 1.

Reply 4: We thank Reviewer A for the opportunity to detail this information. We used the TNM 8th edition because the 9th edition was adopted in our practice after first patients' inclusion in the study.

Changes in the text: Edition of the TNM classification as well as the Stage III subtype was added in Table 1. We also added that information in the material and methods section in line 110 "(based on 8th edition of IASCL TNM)".

Comment 5: Specify the radiological criteria used for assessment of efficacy (RECIST 1.1, iRECIST, irRECIST ...)

Reply 5: We used RECIST v1.1

Changes in the text: line 117 : "(RECIST v1.1)"

Comment 6: Specify the number of planned cycles of immunotherapy according to the therapeutic program (rows 105-107).

Reply 6: The number of planned cycles of immunotherapy vary between the different centers from 2 to 4 years

Changes in the text: line 124-125 : "The number of planned cycles of immunotherapy vary from 2 to 4 years and was based on physician decision."

Reviewer B

Global comment: They showed TTDF, but the clinical impact of TTDF after switching to double dose is unknown. Do they consider the median TTDF:

9.21 months to be an effective ICI treatment?

Reply 1: We are grateful for this question from reviewer B. We recognize that TTDF is a variable whose clinical impact has not been thoroughly evaluated in the literature. However, the primary aim of this endpoint is to provide a descriptive account of double dose usage. The rationale behind starting TTDF on Day 1 of the double dose is to assess its impact on tumor control and patient safety. The timing of transitioning to the double dose varies widely among centers and practitioners, depending on individual patient clinical scenarios, as there are no official guidelines. A patient who switched to the double dose but then ceased ICI quickly due to completing their regimen without relapse until the censoring date was considered successful, as the switch did not alter their treatment strategy (no premature cessation, maintained tumor control). In fact, we already stated this limitation in our discussion.

The TTDF from the time the ICI was initiated should also be indicated, as there is no consistency in when the double dose was initiated.

Reply 2: We indicated in our original manuscript the median duration of immunotherapy before switching (7.7 months) which serves as an indicator of prior exposure (line 148-149).

Major comments:

Comment 1: In Supplemental Table 1, why did they evaluate only three variables in relation to toxicity? Please assess the association of toxicity with other variables such as gender, tissue type and age.

Reply 1: We thank reviewer B for this question. We choose to focus *a priori* on these three variables because:

- In the Higashiyama's study to which we've responded in a letter previously: there was a warning signal on toxicity (>38% in the first cycles, high pulmonary toxicity rate). In their cohort 75% of the population was PDL1 >50%, so we wanted to see this variable in our cohort
- We looked at the molecule because:

* In Higashiyama and al study: only pembrolizumab was described and there were a high rate of toxicity.
* In Hijmering and al study: there were more irAEs in the pembrolizumab group *"Only in the pembrolizumab EI dosing cohort, more AEs were observed compared to SD (p = 0.02)"*

- We looked at the smoking status because of the study *Shankar et al, JAMA oncol 2020 (meta-analysis, 25 studies, 6696 patients)* which found a link between smoking (active or weaned) and a higher risk of immuno-mediated adverse events.

As requested, association of toxicity with other variables such as gender, tissue type and age have been added in the supplemental data.
Changes in the text: Supplemental Table 3 + Line 190

Comment 2: In Supplemental Table 2, they observed a significant association between the cause of failure and the PD-L1 status (p value = 0.011). This analysis is not meaningful. They should investigate the association between PD-L1 expression and toxicity discontinuation rates. In this study, 66 cases have PD-L1≥50% and 30 cases have <50%. Toxicity discontinuation rates were 10.0% (3/30) in PD-L1<50% and 18.2% (12/66). Probably no statistical difference.

Reply 2: We appreciate Reviewer B for providing us with the opportunity to address this matter. Indeed, we had the same question over this analysis, and we specifically discussed it with the statistician. We wanted to know whether this difference with the cause of failure was linked to the rate of toxicity discontinuations or to progression. Using a Bonferroni adjustment, as this was multiple comparisons, there was no significant difference between the distribution of PD-L1 status and progression / toxicity discontinuation.

Here is this analysis:

Variable	**Other**	**Progression**	**Toxicity**	***p***
Cause of failure according to PDL1 status	13 (1)	30 (5)	15 (4)	*p = 0.0114 (F)*
<50%	2 (15.4%)	17 (56.7%)	3 (20.0%)	
>=50%	11 (84.6%)	13 (43.3%)	12 (80.0%)	

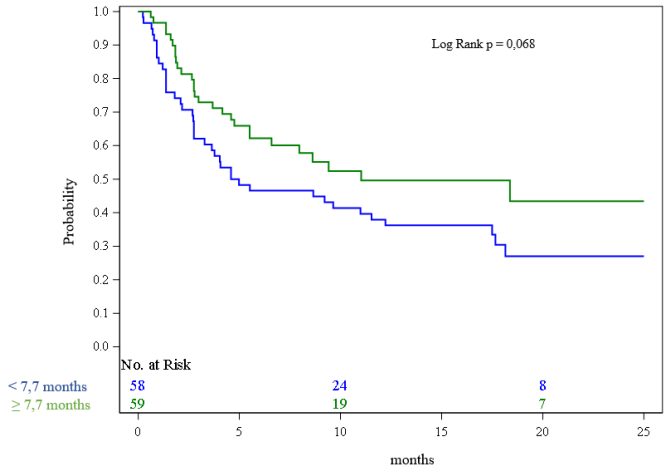
p12	*p13*	***p23***
p = 0.0566	*p = 1.0000*	***p = 0.0822***

* Qualitative results are expressed as: total number (NA), number (%) for each category and the following tests were used: Chi2 (K) or Fisher (F) tests.
p12, p13 and p23 are the p values calculated with the Bonferroni correction.
p12 = p value of the comparison of the distribution of PDL 1 between other reasons and progression.
p13 = comparison of the distribution of PDL 1 between other reasons and toxicity.
p23 = comparison of the distribution of PDL 1 between progression and toxicity.

In fact, the toxicity (all grades) under Double dose neither had a statistical link with PDL1 status (see suppl table 3).
Changes in the text: Line 165-168 "Using Bonferroni adjustment, there were no difference of distribution of PD-L1 status between progression and toxicity even if there was a trend to observe more toxicity-induced failure among the patients with PDL1 TPS≥50% (p value 0.08) – Line 216-220 "We found a statistically significant association between the cause of failure and PD-L1 status (p value = 0.0114), with a trend but not significant toxicity induced failure among patients with PD-L1≥50% (p value = 0.08). However, there was no statistical association between toxicity under DD regimen (all grades) and PD-L1 status".

Comment 3: PD-L1 expression rate is high in the analysed population. PD-L1 high expression is associated with longer PFS. Therefore, I believe that the timing of the switch to double dose is more likely. The significance of the TTDF shown in this population is unclear due to the bias in the population.
Reply 3: We agree with reviewer B and already highlighted this limitation in the discussion section (line 195-199). We do have a cohort with a high rate of patients PDL1>50%. As mentioned in the discussion section, the French regulatory authorization for Pembrolizumab notably is broader in PDL1>50% population as we can use it in 1st line monotherapy. Indeed, 53 patients were in 1st line whom 48 had a PDL1>50% authorizing a monotherapy of immunotherapy. We acknowledge that it represents a selection biais but it is in line with real-life practice. We agree that it might partly explain the long TDDF shown in our study.

Comment 4: There is some data not shown. Lines 141-142, "There was no statistical correlation between TDDF and time of prior exposition to immunotherapy before switching (p value = 0.97)"
Reply 4: We thank reviewer B for this valuable comment. We extensively deliberated among the authors to present or not a figure related to this result. Indeed, we tested the link between prior exposition and TDDF cutting the cohort in two populations: + or – than 7.7 months of prior exposition which is the cohort's median (see below the corresponding figure). As there was no statistical difference, we choose to only cite this result without the corresponding figure in our manuscript. However, based on reviewer B recommendation we added the figure below in the supplemental data (Supplemental Figure 3)



Changes in the text: Ligne 161-164 “There was no statistical correlation between TDDF and median time of prior exposition to immunotherapy before switching (p value = 0.068) “ + Supplemental Figure 3

Minor comments:

Comment 5: They evaluated the survival rate at 12 and 18 months. Please show the Kaplan-Meier curve for OS. In addition, please show the definition of OS.

Reply 5: We thank reviewer B for this sensible comment. We did not analyze overall survival (OS) with Double Dose regimens for several reasons. Indeed, OS is not an ideal criterion in our retrospective work because our cohort includes patients with different treatment (monotherapy or along with chemotherapy) and different oncological situations (first or second line and more). Overall survival may require long-term follow-up and may be influenced by external factors (such as subsequent treatments) and therefore be less sensitive in detecting differences in the efficacy / tolerability of Double Dose. The aim of our work is rather to use a composite parameter influenced by multiple factors (efficacy, toxicity, patient preference, physician reluctance) to capture more rapidly patients in whom the double-dose switch is not effective and/or toxic. This is an earlier endpoint than overall survival, including discontinuations due to tolerability issues, which is closer to real-life objectives. Some studies highlight that Time to treatment discontinuation has become an important surrogate efficacy endpoint especially in real-word studies with a good correlation to endpoints as PFS (Line 300 -304). We did record D1 of Double Dose and patient's vital status at 12 and 18 months from switch for each patient. This shows that our cohort’s size remained sufficiently high throughout follow-up.

Changes in the text: Line 132 “The survival rate at 12 and 18 months indicate the percentage of patients still alive 12 and 18 months after switching for a Double

Dose."

Comment 6: Overall, Typographical errors with hyphens and dots are noticeable. Please correct them.

Reply 6: Thank you for your comment. We've corrected some typographical errors.

Comment 7: In this manuscript, Supplemental Table 1 appears after Supplemental Tables 2 and 3. Please replace the order of the supplemental tables.

Reply 7: Thank you for your attention, it's been corrected.

Changes in the text: See supplementary data legends.

Comment 8: In Supplemental Table 3, Grade 1-"22" is a typo.

Reply 8: Thank you for your attention, it's been corrected.

Changes in the text: See Supplemental Table 2

Comment 9: Line 124, "stage 4 diseases (82%)". This result is not consistent with Table 1. 4 should be marked as IV.

Reply 9: Thank you for your attention, it's been corrected.

Changes in the text: Line 145