



**HAL**  
open science

## Baseline [(18)F]FDG PET features are associated with survival and toxicity in patients treated with CAR T cells for large B cell lymphoma

E Marchal, X Palard-Novello, F Lhomme, M-E Meyer, G Manson, A Devillers, J.-P. Marolleau, R Houot, A Girard

### ► To cite this version:

E Marchal, X Palard-Novello, F Lhomme, M-E Meyer, G Manson, et al.. Baseline [(18)F]FDG PET features are associated with survival and toxicity in patients treated with CAR T cells for large B cell lymphoma. *European Journal of Nuclear Medicine and Molecular Imaging*, 2024, 51 (2), pp.481-489. 10.1007/s00259-023-06427-6 . hal-04227916

HAL Id: hal-04227916

<https://hal.science/hal-04227916v1>

Submitted on 11 Dec 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

BASELINE [<sup>18</sup>F]FDG PET FEATURES ARE ASSOCIATED WITH SURVIVAL AND TOXICITY  
IN PATIENTS TREATED WITH CAR T-CELLS FOR LARGE B-CELL LYMPHOMA

**Authors**

*E Marchal (1), X Palard-Novello (2), F Lhomme (3), ME Meyer (1), G Manson (3), A Devillers (4), JP Marolleau (5), R Houot (3), A Girard (1)*

*E Marchal, X Palard-Novello, R Houot, and A Girard contributed equally to the work*

**Affiliations**

1. Department of Nuclear Medicine, Amiens-Picardie University Hospital, Amiens, France.
2. Univ Rennes, Department of Nuclear Medicine, CLCC Eugène Marquis, INSERM, LTSI - UMR 1099, Rennes, France.
3. Department of Clinical Hematology, Rennes University Hospital, Rennes, France.
4. Department of Nuclear Medicine, CLCC Eugène Marquis, Rennes, France.
5. Department of Hematology, Amiens-Picardie University Hospital, Amiens, France.

**Corresponding author:**

Dr Etienne MARCHAL (ORCID: 0000-0001-7165-4755)

Department of Nuclear Medicine, Amiens-Picardie University Hospital, Amiens, France.

e-mail: [marchal.etienne@chu-amiens.fr](mailto:marchal.etienne@chu-amiens.fr)

## ABSTRACT

**Purpose** – Chimeric antigen receptor (CAR) T-cells have established themselves as an effective treatment for refractory or relapsed large B-cell lymphoma (LBCL). Recently, the sDmax, which corresponds to the distance separating the two farthest lesions standardized by the patient's body surface area, has appeared as a prognostic factor in LBCL. This study aimed to identify [<sup>18</sup>F]FDG-PET biomarkers associated with prognosis and predictive of adverse events in patients treated with CAR T-cells.

**Methods** – Patients were retrospectively included from two different university hospitals. They were being treated with CAR T-cells for LBCL and underwent [<sup>18</sup>F]FDG-PET just before CAR T-cell infusion. Lesions were segmented semi-automatically with a threshold of 41% of the maximal uptake. In addition to clinico-biological features, sDmax, total metabolic tumor volume (TMTV), SUVmax, and uptake intensity of healthy lymphoid organs and liver were collected. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method. The occurrence of adverse events, such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), was reported.

**Results** – Fifty-six patients were included. The median follow-up was 9.7 months. Multivariate analysis showed that TMTV (cut-off of 36 mL) was an independent prognostic factor for PFS ( $p < 0.001$ ) and that sDmax (cut-off of  $0.15 \text{ m}^{-1}$ ) was an independent prognostic factor for OS ( $p = 0.008$ ). Concerning the occurrence of adverse events, a CRP level  $> 35 \text{ mg/L}$  ( $p = 0.006$ ) and a liver SUVmean  $> 2.5$  ( $p = 0.027$ ) before CAR T-cells were associated with grade 2 to 4 CRS and a spleen SUVmean  $> 1.9$  with grade 2 to 4 ICANS.

**Conclusion** – TMTV and sDmax had independent prognostic values, respectively on PFS and OS. Regarding adverse events, the mean liver and spleen uptakes were associated with the occurrence of grade 2 to 4 CRS and ICANS, respectively. Integrating these biomarkers into the clinical workflow could be useful for early adaptation of patients management.

**Keywords** - large B-cell lymphoma; CAR T-cells; positron emission tomography; fluorodeoxyglucose; prognostic factors; sDmax

## INTRODUCTION

Large B-cell lymphoma (LBCL) is the most common type of non-Hodgkin's lymphoma. Its aggressiveness justifies its initial management by a combination of immuno-chemotherapy, after which a third of patients relapse [1]. First approved in 2017, anti-CD19 chimeric antigen receptor (CAR) T-cells are an innovative treatment for refractory or relapsed LBCL [2]. In this setting, CAR T-cells provide a 40%-60% response rate. Cytokine release syndrome (CRS) and immune effector cell associated-neurotoxicity syndrome (ICANS) are common treatment toxicities that often require management in the intensive care unit and are associated with high inflammatory markers in patients [3]. Identification of potential non-responders and patients at high risk of severe toxic syndromes before initiation of treatment would allow for the early management of treatment and subsequent toxicities.

[<sup>18</sup>F]FDG-PET/CT is a cornerstone imaging tool in managing LBCL and evaluating the response to treatment [4]. The total tumor metabolic volume (TMTV) is one of the best prognostic factors for overall survival (OS) in patients with LBCL who received a first-line treatment of chemotherapy combined with monoclonal antibodies, such as R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) [5]. A few studies have investigated prognostic features from [<sup>18</sup>F]FDG-PET performed before LBCL treatment with CAR T-cells, where TMTV values [6,7], maximal tumor uptake (SUVmax) [8], and clinico-biological features such as CRP, LDH, ECOG status [6–8] were highlighted as prognostic factors for OS. Since 2020, sDmax is a new feature measured on PET, defined by the distance separating the two most distant lesions standardized on the body surface [9]. This simple feature has been reported as a prognostic factor in LBCL [10,11], but, to the best of our knowledge, has never been evaluated before treatment with CAR T-cells. Concurrently, [<sup>18</sup>F]FDG-PET/CT provides information regarding the metabolism of healthy immune system structures, which is known to be involved in adverse events induced by CAR T-cells.

The main objective of this study was to investigate the prognostic value of features measured on [<sup>18</sup>F]FDG-PET performed before treatment with CAR T-cells, in particular sDmax in patients with LBCL. We also evaluated the predictive value of the uptake intensity of healthy lymphatic structures on the occurrence of toxicities induced by CAR T-cells.

## MATERIAL AND METHODS

### Study population

The populations of two French university hospitals were retrospectively included. Patients were included in the study if they were treated with CAR T-cells as part of the management of LBCL, between 01/10/2018 and 31/10/2021 and had performed an [<sup>18</sup>F]FDG-PET/CT scan before the CAR T-cells infusion and, if applicable, after bridge chemotherapy. Non-inclusion criteria were unrecoverable or uninterpretable [<sup>18</sup>F]FDG-PET/CT, people under guardianship or curatorship or deprived of liberty.

### **PET/CT protocols and analysis**

[<sup>18</sup>F]FDG-PET/CT was performed within an average of  $15 \pm 7$  days before the administration of CAR T-cells. The mean blood glucose at the time of intravenous injection of [<sup>18</sup>F]FDG was 5.65 mmol/l (standard deviation  $\pm 0.67$ ). The injected activity was on average  $3.03 \pm 0.12$  MBq/kg. The mean time between injection and PET acquisition was  $71 \pm 8$  min. Each PET was pseudonymized and then analyzed using LIFEx v7.2 software [12]. A single nuclear physician carried out image processing. Each lesion was delineated and then segmented according to the threshold of 41% of the SUVmax of each lesion, in accordance with the recommendations of the EANM [13]. The values of the following features were automatically obtained for each PET scan: the distance separating the two farthest lesions, standardized according to the body surface area (sDmax, in  $m^{-1}$ ); the TMTV (mL) defined as the sum of every individual lesion metabolic volume; and SUVmax. A predefined spherical VOI was placed in the liver (4mL), spleen (4mL), bone marrow (1mL x 4), tonsils (1mL), lymph nodes (1mL), and vascular activity (4mL) (Figure 1). The SUVmax and SUVmean of these tissues were measured.

### **Assessment of response and toxicity**

The response to treatment with CAR T-cells was defined by the 2014 Lugano criteria through the reading of follow-up [<sup>18</sup>F]FDG-PET scans performed 1 month and 3 months after the CAR T-cells infusion [14]. The objective response (OR) was defined as the presence of a partial or complete response. Early progression (EP) was defined as disease relapse or progression within 3 months of reinjection of CAR T-cells. Progression-free survival (PFS) was defined as the time between the date of CAR T-cell injection and disease relapse/progression or death from any cause. OS was defined as the time between the date of injection of CAR T-cells and death from any cause. The occurrences of CRS and ICANS were collected in the medical records of patients. Severity was scored from 1 to 4 based on the classification of the American Society for Transplantation and Cellular Therapy (ASTCT) [15]. The delay between the treatment and the toxic syndrome, the management of the patient in the intensive care unit, and the administration of corticosteroid therapy or tocilizumab (anti-IL-6), were registered.

## Statistical analysis

Statistical tests and graphical representations were performed using MedCalc software version 12.5.0.0 (© MedCalc Software Ltd) and R version 4.1.3 (2022-03-10) (© The R Foundation for Statistical Computing). The descriptive statistics of the population were reported according to their frequencies, their means accompanied by their standard deviations (SD), or their medians with interquartile ranges (IQR). The values of the studied prognostic features were dichotomized according to thresholds picked up from the literature for the studied clinical features (ECOG-PS 2-3 versus 0-1 [8,10,16,17], AA stage III-IV versus I-II [10,17], IPI 3-5 versus 0-2 [6,10,17,18], aaIPI 2-3 versus 0-1 [18]). For PET and biological features, no consensual or reproducible threshold values have been reported in the literature in this population. Thus, optimal threshold calculations were performed by maximizing Youden indices, after calculating receiver operating characteristic (ROC) curves with each feature. For the analyses regarding the prognostic value of the studied features, the best threshold was calculated on ROC curves for early progression. For the analyses regarding the prediction of adverse events, the best threshold was calculated on ROC curves for grade 2 to 4 CRS. These threshold values were applied for all the analyses. PFS and OS were estimated using the Kaplan-Meier method, and the comparison between categories was performed using the log-rank test. The selection of prognostic features for OS and PFS was made by univariate and stepwise multivariate analysis using the Cox proportional model. The predictive and prognostic value of features on objective response, early progression, and the occurrence of adverse effects were analyzed using univariate and stepwise multivariate logistic regression. The Spearman correlation coefficients ( $\rho$ ) were reported for each pair of variables highlighted with prognostic value. The statistical tests were two-sided, and their results were considered statistically significant if  $p < 0.05$ .

## RESULTS

### Sample characteristics

Fifty-six patients were analyzed. Clinical and biological characteristics are detailed in Table 1. The median TMTV was 11.5mL [IQR 2.0-56.9]. The median follow-up was 9.7 months [IQR 6.0-20.9]. Forty-five (80%) patients demonstrated an objective response to treatment. Sixteen (29%) patients progressed within the first 3 months. Twenty-three (41%) patients progressed during their follow-up and 19 (24%) died. After 1 year of follow-up, PFS was 54% and OS was 66%.

### Prognostic value

Regarding the OR, in univariate analyses, Ann-Arbor stage III-IV, aaIPI score  $\geq 2$ , TMTV  $> 36$  mL, and sDmax  $> 0.15$  m<sup>-1</sup> were significantly negatively associated with the OR (Table 2). In a multivariate analysis, only the aaIPI score was independently associated with the OR. The area under the ROC curve (AUC) was 0.74 [95%CI 0.60; 0.85]. Regarding the occurrence of EP, the univariate analysis showed that TMTV  $> 36$  mL, aaIPI score  $\geq 2$ , sDmax  $> 0.15$  m<sup>-1</sup>, and SUVmax  $> 15$  were significantly associated with EP (Table 2). In a multivariate analysis, only TMTV  $> 36$ mL was independently associated with EP (AUC 0.66 [95%CI 0.52; 0.78]).

Concerning survival, the features significantly associated with the PFS according to univariate linear regression were the aaIPI score  $\geq 2$ , the LDH level  $> 200$ , the SUVmax  $> 15$ , the TMTV  $> 36$  mL, and the sDmax  $> 0.15$  m<sup>-1</sup> (Table 2). In a multivariate analysis, only the TMTV  $> 36$  mL was independently associated with PFS ( $p < 0.001$ ). The median PFS was significantly longer ( $p < 0.001$ ) in the group of patients with TMTV  $\leq 36$  mL (not reached) compared to that of patients with TMTV  $> 36$  mL (2.8 months) (Figure 2). Features significantly associated with the OS according to univariate linear regression were Ann-Arbor stage III-IV, TMTV  $> 36$  mL, and sDmax  $> 0.15$  m<sup>-1</sup> (Table 2). In a multivariate analysis, only sDmax  $> 0.15$  m<sup>-1</sup> was independently associated with OS ( $p = 0.007$ ). The median OS was significantly longer ( $p = 0.005$ ) in the group of patients with sDmax  $\leq 0.15$  m<sup>-1</sup> (not reached) compared to that of patients with sDmax  $> 0.15$  m<sup>-1</sup> (17.9 months) (Figure 2).

Significant pairwise correlations were found between TMTV, sDmax, and aaIPI, as follows: sDmax with TMTV ( $\rho = 0.74$ ;  $p < 0.001$ ), sDmax with aaIPI ( $\rho = 0.61$ ;  $p < 0.001$ ), and TMTV with aaIPI ( $\rho = 0.58$ ;  $p < 0.001$ ).

### **Prediction of adverse events**

Features significantly associated with the occurrence of grade 2-4 CRS according to univariate analysis were the hepatic SUVmean  $> 2.5$ , the average tonsil SUVmax  $> 1.9$ , and the CRP  $> 35$  mg/L. In a multivariate analysis, the CRP  $> 35$  mg/L ( $p = 0.006$ ) and the hepatic SUVmean  $> 2.5$  ( $p = 0.027$ ) were both features independently associated with the occurrence of CRS grade 2 to 4. The probability of occurrence of grade 2 to 4 CRS varied significantly according to a 3-level score (0, 1, or 2 criteria) based on CRP variables and liver SUVmean ( $p = 0.002$ ; Chi<sup>2</sup> test). The probability of occurrence of CRS grade 2 to 4 was 19.4% (6/31) when patients had a score equal to 0 (CRP  $\leq 35$  mg/L and hepatic SUVmean  $\leq 2.5$ ), 52.4 % (11/21) with a score of 1 (CRP  $> 35$  mg/L or hepatic SUVmean  $> 2.5$ ) and 100% (4/4) with a score of 2 (CRP  $> 35$  mg/L and hepatic SUVmean  $> 2.5$ ) (Figure 3).

The only feature significantly associated with the occurrence of grade 2-4 ICANS according to univariate and multivariate analyses was the spleen SUVmean  $> 1.9$  ( $p = 0.026$ ) (Table 3).

## DISCUSSION

In this study, we explored the value of [ $^{18}\text{F}$ ]FDG-PET features obtained before CAR T-cells therapy. When studying the prognostic value of features related to tumors, the sDmax was found as the only feature independently associated with OS. When investigating the metabolic activity of healthy structures of the immune system for predicting the occurrence of immune-related adverse events, a 3-point scale score integrating the mean hepatic SUV ( $> 2.5$ ) and the CRP blood level ( $> 35$  mg/L) was associated with the probability of occurrence of grade 2 to 4 CRS. To the best of our knowledge, this is the first study to investigate the prognostic value of the sDmax in this population, as well as the value of PET features to predict adverse events.

In previous studies performed in populations of LBCL patients treated with chemotherapy, the sDmax showed its independent prognostic value, with thresholds ranging from 5.7 cm to 58 cm for the Dmax and from  $0.25\text{ m}^{-1}$  to  $0.32\text{ m}^{-1}$  for the sDmax [9,10,16,19]. In our study, the most discriminating sDmax threshold was  $0.15\text{ m}^{-1}$ , slightly lower than previously published values from different populations. The other prognostic features for OS that were reported as independent in the literature but not found in our study are TMTV [6,7,9,16], LDH level [6,8], the number of extranodal sites [7], tumor SUVmax [6], ECOG-PS stage [8,10] and CRP level [7].

The only independent prognostic factor for progression (early progression and PFS) in our study was TMTV  $> 36\text{mL}$ . TMTV is found indirectly associated with progression in most published studies in patients with LBCL [5,6,9,10,16,19,20]. The other independent prognostic factors for progression reported in the literature are the LDH level [6] and the number of extra-nodal sites [7], tumor SUVpeak [19], (s)Dmax [10,16,19], Ann-Arbor stage [21], ECOG-PS status [10,16], and CRP level [7]. Although TMTV and sDmax were never found together as independent prognostic features after stepwise multivariate analysis in our study, they both were significantly associated with OR, EP, PSF, and OS in univariate analyses. The moderate to strong correlation between these two factors ( $\rho=0.74$ ) may have prevented from showing independent prognostic values in multivariate analyses [22]. In contrast, there was no correlation between the sDmax and the TMTV in the series reported by Cottreau et al. [9,10,16]. Analyses with greater statistical power (i.e., a larger sample size) might have revealed complementary prognostic values of these two features since they are related to different aspects of disease severity. While TMTV is an indicator of tumor burden, sDmax is a marker of tumor spread. The variability of the methods of measurement and dichotomization of the features between the studies may explain some differences in the results. Concerning the sDmax, we chose to use the maximum Euclidean distance between the two furthest lesion voxels standardized by the body surface because this feature previously showed its independent prognostic value before chemotherapy on OS and PFS [10]. Some other authors have used the distances between the centers



of gravity of the furthest lesions [9,10]. On the cohort of 291 patients from the REMARC trial, a high sDmax remained a factor of poor prognosis regardless of its method of calculation [10]. The sDmax dichotomization thresholds before chemotherapy vary in the literature between 0.25 and 0.32 m<sup>-1</sup> [10,16]. In our study, the bridge chemotherapy provided before the PET scan presumably reduced the tumor volume, which may explain a lower sDmax dichotomization threshold than in other recently published studies. Regarding TMTV, in our study, we chose a tumor delineation threshold set at 41% of the SUVmax of each lesion, in accordance with the recommendations of the EANM [13], and with most of the recent studies published on this subject [5,6,9,10,16,19,20]. Among the studies that demonstrated a prognostic impact of TMTV with a threshold of 41%, the dichotomization thresholds that made it possible to separate the groups with good and poor prognosis varied from 220 mL to 394 mL before chemotherapy treatment [9,10,16] and 25 mL to 80 mL before CAR T-cells [6,7,20]. Thus, the optimal threshold calculated at 36 mL in our study was in the same range as those published in similar populations. Some of the variations between the presented results and those of previously published studies investigating predictive features in LBCL factors before CART T-cells can also be explained by differences in the included populations, regarding: the tumor volume (50% of patient had a TMTV > 11.5mL in the present sample, vs. 50% > 52mL [7] and 44% > 80 mL [6] in previous studies), the number of previous systemic treatment lines received (with a median of 2 prior lines in the present sample vs. 3 in previous studies [6–8]), and the type of CAR T-cells patients received (axi-cel in 89% of the present sample vs. 58%-59% in previous studies [6–8]). This latter might have a substantial impact on the results since axi-cel has shown better efficacy than tisa-cel on overall survival [23].

The prediction of grade  $\geq 2$  adverse effects according to the ASTCT classification would make it possible to anticipate an adaptation of management [24,25]. We hypothesized that the activation of the healthy structures of the immune system measured by their [<sup>18</sup>F]FDG uptake could help in predicting immune-related adverse events. In this study, we found the hepatic SUVmean (> 2.5) as independently associated with the occurrence of CRS grade 2 to 4, and the spleen SUVmean (> 1.9) as significantly associated with the occurrence of grade 2-4 ICANS. The spleen has a well-known key role in producing and growing immune cells. The liver allows the maturation of multiple lymphocytes and appears to be progressively integrated among the group of lymphoid organs [26]. This has a role in the regulation of systemic inflammation, via interleukin 6 [27–29]. The elevation of IL-6 after reinjection of CAR T-cells is associated with more severe CRS [30], frequently treated with anti-IL-6 (tocilizumab) [31]. Hepatic inflammation is a provider of impaired hepatic homeostasis [32] and increased [<sup>18</sup>F]FDG uptake [33,34], which may explain its association with the severity of CRS. To date, to the best of our knowledge, only

one study involving 10 patients has been published evaluating the value of measuring the [<sup>18</sup>F]FDG uptake of healthy lymphatic structures in this context [35]. Derlin et al. highlighted the association between the response to treatment and the evolution of the uptake of the spleen and lymph nodes on [<sup>18</sup>F]FDG-PET 1 month after the CAR T-cells infusion. They did not have evidence of any association with the occurrence of adverse effects. In other settings, it has been widely reported that [<sup>18</sup>F]FDG uptake of lymphoid organs is higher in infectious, inflammatory, and/or hematopoietic regeneration contexts [36–38].

This study has several limitations. The first is its retrospective design. Secondly, the segmentation of the lesions was carried out by a single nuclear physician, which does not take into account the inter-observer variability of measurements. Nevertheless, the measurement of TMTV with a relative threshold of 41% recommended by the EANM has been described as having excellent inter-observer reproducibility (intraclass correlation coefficient > 0.96) within cohorts [39,40]. This suggests that a double-blind reading of the PET scans would not have substantially modified our results. Conversely, there is variability in the 41% TMTV thresholds used to define the prognostic groups according to the studies, ranging from 25 mL to 80 mL in cohorts of patients treated for LBCL before treatment with CAR T-cells [6,7,20]. This variability may hinder the use of TMTV in everyday clinical practice. To the best of our knowledge, no study has been published yet concerning the inter-observer variability of sDmax.

In our study, as in most of the studies published on the subject, the pre-treatment [<sup>18</sup>F]FDG PET/CT scans were performed at “time-to-treat” (PET-TT), after a possible bridge and just before the CAR T-cells infusion [6,7,17,20]. Some other authors have chosen to study PET/CT scan at “time-of-decision” (PET-TD), performed before a possible bridge, at the time of the therapeutic decision [8]. Lesion features from PET have been reported as having a prognostic value, whether performed before or after a possible bridge. While Cohen et al. reported a prognostic value of SUVmax on PET-TD [8], TMTV was described as prognostic when measured on PET-TT [6,7,17,20].

## CONCLUSION

In this study, we highlighted the prognostic value of features extracted from [<sup>18</sup>F]FDG-PET/CT performed before the CAR T-cells infusion in patients treated for progressive LBCL after chemotherapy, in particular the sDmax on OS and the TMTV on PFS. Furthermore, combining the intensity of liver [<sup>18</sup>F]FDG uptake with CRP blood level into a 3-point scale score could predict the probability of occurrence of grade 2 to 4 CRS. Subject to the validation of these results in other studies, the generalized use of these features could enable to adapt

the management of patients according to their *a priori* probability of response to treatment and of occurrence of adverse events.

### **Compliance with ethical standards**

#### **Funding**

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

#### **Conflict of interest**

The authors have no financial or proprietary interests in any material discussed in this article.

#### **Ethical approval**

This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

#### **Consent to participate**

Informed consent was obtained from all individual participants included in the study.

#### **Authors contributions**

Conceptualization: Etienne MARCHAL, Antoine GIRARD; Methodology: Etienne MARCHAL, Antoine GIRARD; Formal analysis and investigation: Etienne MARCHAL, Antoine GIRARD, Xavier PALARD-NOVELLO; Writing - original draft preparation: Etienne MARCHAL, Antoine GIRARD, Marc-Etienne MEYER; Writing - review and editing: Antoine GIRARD, Etienne MARCHAL, Xavier PALARD-NOVELLO, Faustine LHOMME, Guillaume MANSON, Marc-Etienne MEYER, Jean-Pierre MAROLLEAU, Roche HOUOT, Anne DEVILLERS; Resources: Antoine GIRARD, Xavier PALARD-NOVELLO, Jean-Pierre MAROLLEAU, Marc-Etienne MEYER, Roche HOUOT, Anne DEVILLERS; Supervision: Antoine GIRARD.

#### **Data availability**

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

## REFERENCES

- [1] Tilly H. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015;26:10.
- [2] Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N Engl J Med* 2017;377:2531–44. <https://doi.org/10.1056/NEJMoal707447>.
- [3] Brudno JN, Kochenderfer JN. Recent advances in CAR T-cell toxicity: Mechanisms, manifestations and management. *Blood Rev* 2019;34:45–55. <https://doi.org/10.1016/j.blre.2018.11.002>.
- [4] Barrington SF, Mikhaeel NG, Kostakoglu L, Meignan M, Hutchings M, Müller SP, et al. Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group. *J Clin Oncol* 2014;32:3048–58. <https://doi.org/10.1200/JCO.2013.53.5229>.
- [5] Vercellino L, Cottreau A-S, Casasnovas O, Tilly H, Feugier P, Chartier L, et al. High total metabolic tumor volume at baseline predicts survival independent of response to therapy. *Blood* 2020;135:1396–405. <https://doi.org/10.1182/blood.2019003526>.
- [6] Galtier J, Vercellino L, Chartier L, Olivier P, Tabouret-Viaud C, Mesguich C, et al. PET-imaging assessment for guiding strategy in patients with relapsed/refractory large B-cell lymphoma receiving CAR T-cells. *Haematologica* 2022. <https://doi.org/10.3324/haematol.2021.280550>.
- [7] Vercellino L, Di Blasi R, Kanoun S, Tessoulin B, Rossi C, D’Aveni-Piney M, et al. Predictive factors of early progression after CAR T-cell therapy in relapsed/refractory diffuse large B-cell lymphoma. *Blood Adv* 2020;4:5607–15. <https://doi.org/10.1182/bloodadvances.2020003001>.
- [8] Cohen D, Luttwak E, Beyar-Katz O, Hazut Krauthammer S, Bar-On Y, Amit O, et al. [18F]FDG PET-CT in patients with DLBCL treated with CAR-T cell therapy: a practical approach of reporting pre- and post-treatment studies. *Eur J Nucl Med Mol Imaging* 2022;49:953–62. <https://doi.org/10.1007/s00259-021-05551-5>.
- [9] Cottreau A-S, Nioche C, Dirand A-S, Clerc J, Morschhauser F, Casasnovas O, et al. <sup>18</sup>F-FDG PET Dissemination Features in Diffuse Large B-Cell Lymphoma Are Predictive of Outcome. *J Nucl Med* 2020;61:40–5. <https://doi.org/10.2967/jnumed.119.229450>.
- [10] Cottreau A-S, Meignan M, Nioche C, Capobianco N, Clerc J, Chartier L, et al. Risk stratification in diffuse large B-cell lymphoma using lesion dissemination and metabolic tumor burden calculated from baseline PET/CT†. *Ann Oncol* 2021;32:404–11. <https://doi.org/10.1016/j.annonc.2020.11.019>.
- [11] Girum KB, Rebaud L, Cottreau A-S, Meignan M, Clerc J, Vercellino L, et al. <sup>18</sup>F-FDG PET Maximum-Intensity Projections and Artificial Intelligence: A Win-Win Combination to Easily Measure Prognostic Biomarkers in DLBCL Patients. *J Nucl Med* 2022;63:1925–32. <https://doi.org/10.2967/jnumed.121.263501>.
- [12] Nioche C, Orlhac F, Boughdad S, Reuzé S, Goya-Outi J, Robert C, et al. LIFEx: A Freeware for Radiomic Feature Calculation in Multimodality Imaging to Accelerate Advances in the Characterization of Tumor Heterogeneity. *Cancer Res* 2018;78:4786–9. <https://doi.org/10.1158/0008-5472.CAN-18-0125>.
- [13] Boellaard R, Delgado-Bolton R, Oyen WJG, Giammarile F, Tatsch K, Eschner W, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. *Eur J Nucl Med Mol Imaging* 2015;42:328–54. <https://doi.org/10.1007/s00259-014-2961-x>.
- [14] Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol Off J Am Soc Clin Oncol* 2014;32:3059–68. <https://doi.org/10.1200/JCO.2013.54.8800>.
- [15] Lee DW, Santomaso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant* 2019;25:625–38. <https://doi.org/10.1016/j.bbmt.2018.12.758>.
- [16] Cottreau A-S, Meignan M, Nioche C, Clerc J, Chartier L, Vercellino L, et al. New Approaches in Characterization of Lesions Dissemination in DLBCL Patients on Baseline PET/CT. *Cancers* 2021;13:3998. <https://doi.org/10.3390/cancers13163998>.
- [17] Zhou Y, Li J, Zhang X, Jia T, Zhang B, Dai N, et al. Prognostic Value of Radiomic Features of <sup>18</sup>F-FDG PET/CT in Patients With B-Cell Lymphoma Treated With CD19/CD22 Dual-Targeted Chimeric Antigen Receptor T Cells. *Front Oncol* 2022;12:834288. <https://doi.org/10.3389/fonc.2022.834288>.
- [18] Garcia-Recio M, Wudhikarn K, Pennisi M, Alonso-Trillo R, Flynn J, Shouval R, et al. The International Prognostic Index Is Associated with Outcomes in Diffuse Large B Cell Lymphoma after Chimeric Antigen Receptor T Cell Therapy. *Transplant Cell Ther* 2021;27:233–40. <https://doi.org/10.1016/j.jtct.2020.10.022>.

- [19] Eertink JJ, van de Brug T, Wiegers SE, Zwezerijnen GJC, Pfaehler EAG, Lugtenburg PJ, et al. 18F-FDG PET baseline radiomics features improve the prediction of treatment outcome in diffuse large B-cell lymphoma. *Eur J Nucl Med Mol Imaging* 2022;49:932–42. <https://doi.org/10.1007/s00259-021-05480-3>.
- [20] Iacoboni G, Simó M, Villacampa G, Catalá E, Carpio C, Díaz-Lagares C, et al. Prognostic impact of total metabolic tumor volume in large B-cell lymphoma patients receiving CAR T-cell therapy. *Ann Hematol* 2021;100:2303–10. <https://doi.org/10.1007/s00277-021-04560-6>.
- [21] Zhu L, Meng Y, Guo L, Zhao H, Shi Y, Li S, et al. Predictive value of baseline <sup>18</sup>F-FDG PET/CT and interim treatment response for the prognosis of patients with diffuse large B-cell lymphoma receiving R-CHOP chemotherapy. *Oncol Lett* 2020;21:132. <https://doi.org/10.3892/ol.2020.12393>.
- [22] Schober P, Boer C, Schwarte LA. Correlation Coefficients: Appropriate Use and Interpretation. *Anesth Analg* 2018;126:1763. <https://doi.org/10.1213/ANE.0000000000002864>.
- [23] Gauthier J, Gazeau N, Hirayama AV, Hill JA, Wu V, Cearley A, et al. Impact of CD19 CAR T-cell product type on outcomes in relapsed or refractory aggressive B-NHL. *Blood* 2022;139:3722–31. <https://doi.org/10.1182/blood.2021014497>.
- [24] Kymriah [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2019. [https://www.novartis.com/us-en/sites/novartis\\_us/files/kymriah.pdf](https://www.novartis.com/us-en/sites/novartis_us/files/kymriah.pdf) n.d.
- [25] Yescarta [prescribing information]. Santa Monica, CA: Kite Pharma Inc; 2019. <https://www.gilead.com/-/media/files/pdfs/medicines/oncology/yescarta/yescarta-pi.pdf> n.d.
- [26] Crispe IN. The Liver as a Lymphoid Organ. *Annu Rev Immunol* 2009;27:147–63. <https://doi.org/10.1146/annurev.immunol.021908.132629>.
- [27] Moshage H. Cytokines and the hepatic acute phase response. *J Pathol* 1997;181:257–66. [https://doi.org/10.1002/\(SICI\)1096-9896\(199703\)181:3<257::AID-PATH756>3.0.CO;2-U](https://doi.org/10.1002/(SICI)1096-9896(199703)181:3<257::AID-PATH756>3.0.CO;2-U).
- [28] Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med* 1999;340:448–54. <https://doi.org/10.1056/NEJM199902113400607>.
- [29] Zhou Z, Xu M-J, Gao B. Hepatocytes: a key cell type for innate immunity. *Cell Mol Immunol* 2016;13:301–15. <https://doi.org/10.1038/cmi.2015.97>.
- [30] Teachey DT, Lacey SF, Shaw PA, Melenhorst JJ, Maude SL, Frey N, et al. Identification of Predictive Biomarkers for Cytokine Release Syndrome after Chimeric Antigen Receptor T-cell Therapy for Acute Lymphoblastic Leukemia. *Cancer Discov* 2016;6:664–79. <https://doi.org/10.1158/2159-8290.CD-16-0040>.
- [31] Le RQ, Li L, Yuan W, Shord SS, Nie L, Habtemariam BA, et al. FDA Approval Summary: Tocilizumab for Treatment of Chimeric Antigen Receptor T Cell-Induced Severe or Life-Threatening Cytokine Release Syndrome. *The Oncologist* 2018;23:943–7. <https://doi.org/10.1634/theoncologist.2018-0028>.
- [32] Robinson MW, Harmon C, O’Farrelly C. Liver immunology and its role in inflammation and homeostasis. *Cell Mol Immunol* 2016;13:267–76. <https://doi.org/10.1038/cmi.2016.3>.
- [33] Keramida G, Potts J, Bush J, Verma S, Dizdarevic S, Peters AM. Accumulation of 18F-FDG in the Liver in Hepatic Steatosis 2014;6.
- [34] Yue X, Wang J, Ye F, Xiao D. Mean standardized uptake value (SUV<sub>mean</sub>) and global hepatic glycolysis as potential imaging markers reflecting hepatic functional capacity: evidence from 18F-FDG PET/CT. *Hippokratia* 2018;22:122–6.
- [35] Derlin T, Schultze-Florey C, Werner RA, Möhn N, Skripuletz T, David S, et al. 18F-FDG PET/CT of off-target lymphoid organs in CD19-targeting chimeric antigen receptor T-cell therapy for relapsed or refractory diffuse large B-cell lymphoma. *Ann Nucl Med* 2021;35:132–8. <https://doi.org/10.1007/s12149-020-01544-w>.
- [36] Patel NH, Osborne MT, Teague H, Parel P, Svirydava M, Sorokin AV, et al. Heightened splenic and bone marrow uptake of 18F-FDG PET/CT is associated with systemic inflammation and subclinical atherosclerosis by CCTA in psoriasis: An observational study. *Atherosclerosis* 2021;339:20–6. <https://doi.org/10.1016/j.atherosclerosis.2021.11.008>.
- [37] Pijl JP, Kwee TC, Slart RHJA, Yakar D, Wouthuyzen-Bakker M, Glaudemans AWJM. Clinical implications of increased uptake in bone marrow and spleen on FDG-PET in patients with bacteremia. *Eur J Nucl Med Mol Imaging* 2021;48:1467–77. <https://doi.org/10.1007/s00259-020-05071-8>.
- [38] Deng L, Liu L, Ding H, Zhang S, Wang W, Zhang W, et al. The Value of Diffuse Splenic and Hepatic 18F-FDG Uptake on PET/CT in Diagnosing Patients with Anemia. *Contrast Media Mol Imaging* 2022;2022:1–7. <https://doi.org/10.1155/2022/3804673>.
- [39] Ilyas H, Mikhaeel NG, Dunn JT, Rahman F, Møller H, Smith D, et al. Defining the optimal method for measuring baseline metabolic tumour volume in diffuse large B cell lymphoma. *Eur J Nucl Med Mol Imaging* 2018;45:1142–54. <https://doi.org/10.1007/s00259-018-3953-z>.
- [40] Tutino F, Puccini G, Linguanti F, Puccini B, Rigacci L, Kovalchuk S, et al. Baseline metabolic tumor volume calculation using different SUV thresholding methods in Hodgkin lymphoma patients: interobserver agreement and reproducibility across software platforms. *Nucl Med Commun* 2021;42:284–91. <https://doi.org/10.1097/MNM.0000000000001324>.



## FIGURES

**Table 1** Patients characteristics before CAR T-cells infusion, and adverse events probability

Features	number (%) or average ( $\pm$ SD)
Patients analyzed	56 (100%)
Sex (male)	36 (64%)
Age	60.2 ( $\pm$ 11.5)
Transformation from previous low grade lymphoma	15 (27%)
Type of CAR T-cells	
• Axi-cel	50 (89%)
• Tisa-cel	6 (11%)
Bridging chemotherapy	46 (82%)
Previous lines of systemic therapy	
• 1	10 (18%)
• 2	27 (48%)
• 3	19 (34%)
Ann-Arbor stage	
• No disease	8 (14%)
• 1-2	14 (25%)
• 3-4	34 (61%)
IPI	
• 0-1	17 (31%)
• 2	18 (32%)
• 3	13 (23%)
• 4-5	8 (14%)
Age-adjusted IPI	
• 0-1	32 (57%)
• 2-3	24 (43%)
LDH	
• Blood level (U/L)	297 ( $\pm$ 123)
• Above the upper normal limit	31 (55%)
CRP > 5mg/L	23 (41%)
Time between PET [ $^{18}$ F]FDG and infusion of CAR T-cells (d)	14.3 ( $\pm$ 6.3)
TMTV (mL)	79.8 ( $\pm$ 104.5)
sDmax (m $^{-1}$ )	0.26 ( $\pm$ 0.25)
SUVmax	13.9 ( $\pm$ 9.7)
Adverse events	51 (91%)
• CRS	
• Grade 0-1	35 (63%)
• Grade 2-4	21 (37%)
• ICANS	
• Grade 0-1	40 (71%)
• Grade 2-4	16 (29%)



**Table 2** Univariate and stepwise multivariate logistic regressions of the prognostic features studied.

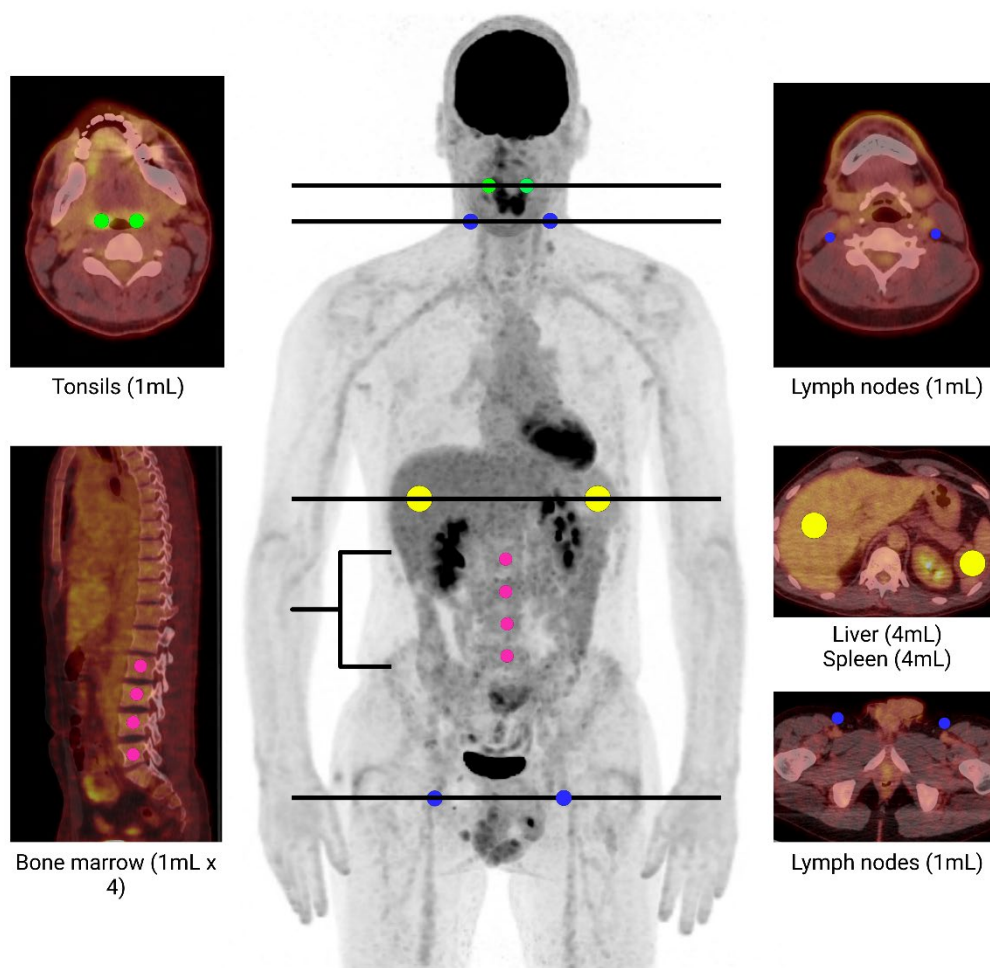
	Objective response			Early progression			Progression-free survival			Overall survival		
	OR (95%CI)	p uni.	p multi.	OR (95%CI)	p uni.	p multi.	HR (95%CI)	p uni.	p multi.	HR (95%CI)	p uni.	p multi.
ECOG-PS 2-3	1.54 (0.17 to 14.28)	0.70	-	1.00 (0.17 to 5.77)	1.00	-	0.52 (0.17 to 1.60)	0.37	-	0.60 (0.18 to 2.00)	0.48	-
AA stage III-IV	<b>0.11</b> <b>(0.01 to 0.97)</b>	<b>0.047</b>	ns	3.92 (0.97 to 15.91)	0.056	-	2.21 (1.01 to 4.85)	0.066	-	<b>3.57</b> <b>(1.51 to 8.42)</b>	<b>0.014</b>	ns
IPI 3-5	0.42 (0.11 to 1.59)	0.20	-	1.44 (0.44 to 4.71)	0.54	-	1.61 (0.71 to 3.63)	0.23	-	1.01 (0.42 to 2.45)	0.98	-
aaIPI 2-3	<b>0.11</b> <b>(0.02 to 0.58)</b>	<b>0.009</b>	<b>0.009</b>	<b>4.57</b> <b>(1.31 to 15.90)</b>	<b>0.017</b>	ns	<b>3.07</b> <b>(1.36 to 6.92)</b>	<b>0.004</b>	ns	1.91 (0.80 to 4.55)	0.14	-
LDH $\geq$ 200	0.22 (0.03 à 1.90)	0.17	-	8.08 (0.96 to 67.7)	0.054	-	<b>3.34</b> <b>(1.43 to 7.78)</b>	<b>0.036</b>	ns	1.34 (0.52 to 3.43)	0.56	-
CRP > 20 mg/L	0.86 (0.19 à 3.83)	0.85	-	0.61 (0.14 to 2.55)	0.50	-	0.76 (0.30 to 1.88)	0.58	-	1.36 (0.49 to 3.78)	0.52	-
SUVmax > 15	0.32 (0.08 à 1.24)	0.099	-	<b>5.13</b> <b>(1.46 to 18.0)</b>	<b>0.010</b>	ns	<b>2.33</b> <b>(1.03 to 5.30)</b>	<b>0.029</b>	ns	1.79 (0.74 to 4.31)	0.18	-
TMTV > 36 mL	<b>0.16</b> <b>(0.040 à 0.67)</b>	<b>0.012</b>	ns	<b>7.86</b> <b>(2.14 to 28.8)</b>	<b>0.002</b>	<b>0.002</b>	<b>4.22</b> <b>(1.59 to 11.2)</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>2.76</b> <b>(0.97 to 7.85)</b>	<b>0.015</b>	ns
sDmax > 0.15 m <sup>-1</sup>	<b>0.21</b> <b>(0.05 à 0.89)</b>	<b>0.034</b>	ns	<b>4.57</b> <b>(1.31 to 15.9)</b>	<b>0.017</b>	ns	<b>2.82</b> <b>(1.24 to 6.41)</b>	<b>0.008</b>	ns	<b>3.25</b> <b>(1.31 to 8.07)</b>	<b>0.005</b>	<b>0.007</b>
EN sites $\geq$ 2	0.50 (0.12 to 2.06)	0.34	-	2.40 (0.67 to 8.59)	0.18	-	1.61 (0.63 to 4.10)	0.26	-	1.56 (0.57 to 4.22)	0.33	-

**Table 3** Univariate and stepwise multivariate logistic regressions of features related to the immune system suspected to be predictive of toxicities.

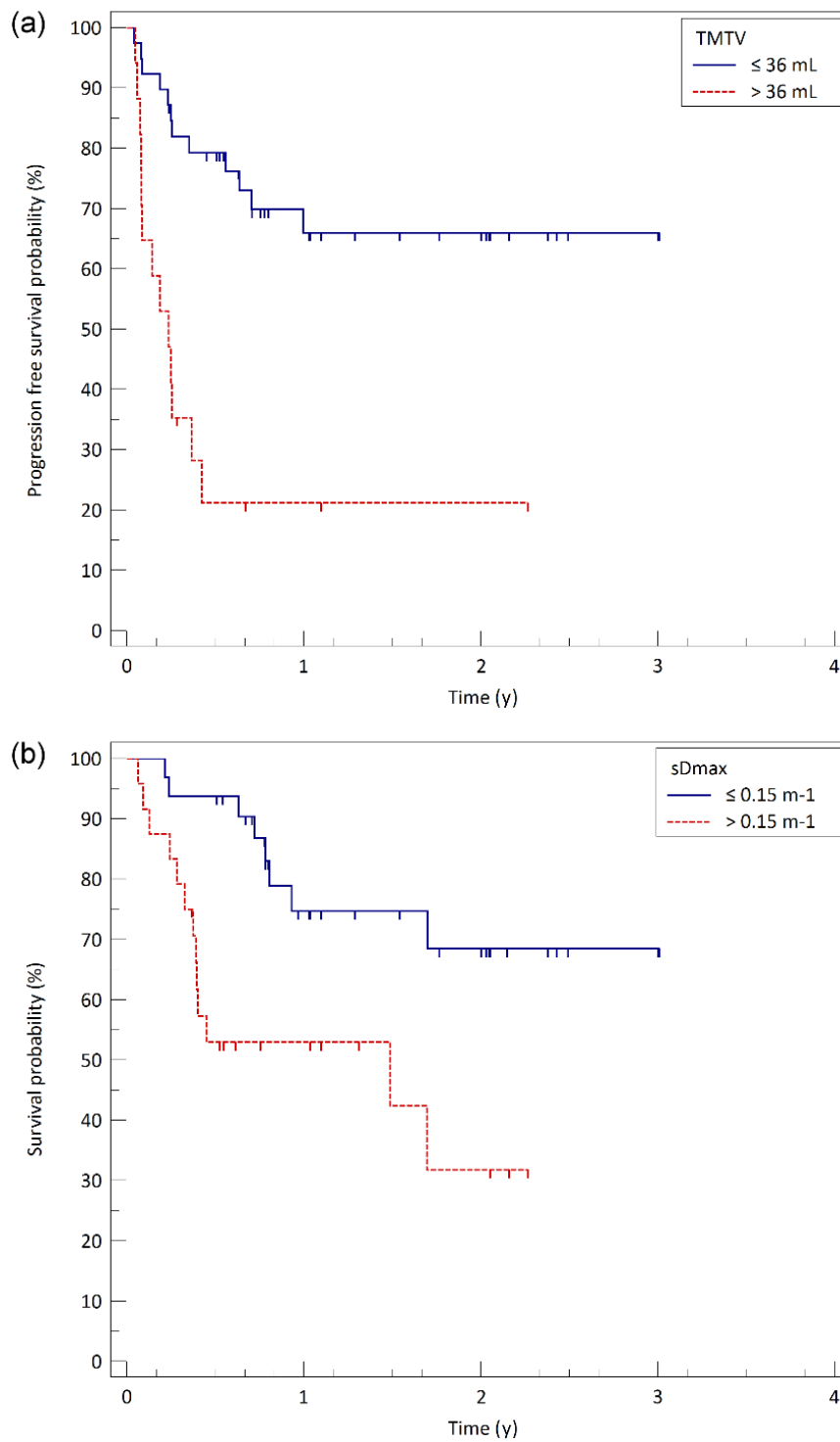
	CRS grade 2 to 4			ICANS grade 2 to 4		
	OR (95%CI)	p uni.	p multi.	OR (95%CI)	p uni.	p multi.
Liver_mean > 2.5	<b>3.7</b> (1.16 to 11.9)	<b>0.025</b>	<b>0.027</b>	2.64 (0.79 to 8.76)	0.12	-
Spleen_mean > 1.9	3.1 (0.95 to 10.1)	0.055	-	<b>4.40</b> (1.19 to 16.3)	<b>0.026</b>	<b>0.026</b>
BM_mean > 3.5	13.4 (0.66 to 274)	0.091	-	5.57 (0.47 to 66.3)	0.16	-
Waldeyer_maxAV > 1.9	<b>4.0</b> (0.99 to 16.2)	<b>0.034</b>	ns	1.44 (0.39 to 5.36)	0.58	-
LN_maxAV > 1.2	1.9 (0.47 to 7.45)	0.37	-	0.57 (0.11 to 3.04)	0.50	-
CRP > 35 mg/L	<b>10.2</b> (1.90 to 54.3)	<b>0.007</b>	<b>0.006</b>	1.10 (0.24 to 4.86)	0.91	-

Liver\_mean: SUVmean of liver; Spleen\_mean: SUVmean of spleen; BM\_mean: bone marrow SUVmean; Waldeyer\_maxAV: mean of tonsils SUVmax; LN\_maxAV: mean of lymph nodes SUVmax.

**Fig. 1** Maximum intensity projections and fused axial slices of a patient in complete response. Delineations of healthy structures of the immune system are indicated in color.



**Fig. 2** Curves of progression-free survival (A) and overall survival (B) according to TMTV and sDmax, respectively.



**Fig. 3** Probability of occurrence of CRS grade 2 to 4 according to a 3-point scale score (presence of 0, 1 or 2 factors among CRP>35 mg/L and SUVmeanLiver>2.5).

