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## Metabolic tumor volume predicts outcome in advanced stage follicular lymphoma patients from the Relevance trial.

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## Title page

Metabolic tumor volume predicts outcome in advanced stage follicular lymphoma patients from the Relevance trial.

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### Highlights

- Baseline TMTV is a strong prognostic factor of POD24 and PFS in advanced FL even in the area of antibody maintenance.
- TMTV combined with FLIPI score identified a subgroup of patients (16%) at high risk of relapse with a 6y-PFS of 41.0%.
- High TMTV patients have similar PFS and POD 24 in both treatment arms.

## Abstract

**Background:** We investigated the prognostic value of baseline PET parameters for patients with treatment-naïve follicular lymphoma (FL) in the phase 3 RELEVANCE trial, comparing the immunomodulatory combination of lenalidomide and rituximab (R<sup>2</sup>) vs R-chemotherapy (R-chemo), with both regimens followed by R maintenance therapy.

**Patients and methods:** Baseline characteristics of the entire PET-evaluable population (n=406/1032) were well balanced between treatment arms. SUVmax and SDmax, the standardized distance between two lesions the furthest apart were extracted. Total metabolic tumor volume (TMTV) was computed using the 41%SUVmax method.

**Results:** With a median follow-up of 6.5 years, the 6y-PFS was 57.8%, the median TMTV was 284 cm<sup>3</sup>, SUVmax 11.28 and SDmax 0.32 m<sup>-1</sup>, with no significant difference between arms. High TMTV (> 510 cm<sup>3</sup>) and FLIPI were associated with an inferior PFS (p=0.013 and p=0.006), whereas SUVmax and SDmax were not (p=0.08 and p=0.12). In multivariable analysis, FLIPI and TMTV remained significantly associated with PFS (p=0.0119 and p=0.0379). These two adverse factors combined stratified the overall population into 3 risk groups: patients with no risk factors (40%), with one factor (44%), or with both (16%), with a 6y-PFS of 67.7%, 54.5% and 41.0% respectively. No significant interaction between treatment arms and TMTV or FLIPI (p=0.31 and p=0.59) were observed. The high risk group (high TMTV and FLIPI 3-5) had similar PFS in both arms (p=0.45) with a median PFS of 68.4% in the R chemo arm vs 71.4 % in the R<sup>2</sup> arm.

**Conclusion:** Baseline TMTV is predictive of PFS, independently of FLIPI, in patients with advanced FL even in the context of antibody maintenance.

**Keywords :** Metabolic tumor volume - Follicular lymphoma – Prognostication – PET/CT – Maintenance therapy

**Key words:** Immediately after the abstract, provide a maximum of 6 key words, using American spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes;



## Introduction

Follicular lymphoma (FL) is the most common indolent lymphoma worldwide, representing around 20% of all adult lymphomas in Europe and 30% in the USA<sup>1</sup>. Most patients with FL have long-term disease control resulting in a prolonged overall survival (OS), beyond 20 years. However, approximately 20% of patients experience disease progression within two years after treatment initiation (POD24) which is associated with a shorter OS of approximately 50% at 5-years<sup>1</sup>. Several indices widely based on simple clinical or biologic parameters have been validated as prognostic markers in FL.

18F-fluorodeoxyglucose positron emission tomography/computed tomography (18FDG-PET/CT) is the recommended gold-standard imaging for staging and response assessment in FDG-avid lymphomas<sup>2,3</sup>. Quantitative 18F-FDG PET/CT parameters such as SUVmax, Total Metabolic Tumor Volume (TMTV)<sup>4</sup> and more recently dissemination features have been evaluated to further refine outcome estimates. In particular, TMTV, reflecting the whole tumor burden has been shown to be a prognostic factor across many lymphoma subtypes<sup>5-8</sup>. In FL, reports of its prognostic impact are less consistent. An initial pooled analysis of three prospective trials<sup>4</sup> including patients mainly treated with the R-CHOP regimen and without maintenance, identified a superior 5y PFS of 65% (55.3 to 73.3) for patients with a low TMTV vs 33% (20.0 to 46.1) for those with a high TMTV, independently from end of induction PET response<sup>9</sup>. Its prognostic value was also shown in two retrospective analyses<sup>10,11</sup>. By contrast, in the GALLIUM trial where the majority of the patients received bendamustine and all received an anti-CD20 antibody maintenance, the impact of TMTV was less clear. While a manually determined TMTV was not demonstrated to be predictive, regardless of threshold method used to define tumour<sup>12</sup>, a fully automated approach based on deep learning algorithms did identify a significant difference, with a 3-year PFS of 85.1% (81.3 to 89.1%) for patients with low TMTV versus 77.3% (71.3 to 83.7%) for those with high TMTV (HR 1.59;  $p < 0.013$ )<sup>13</sup>. The predictive value of TMTV in chemo-free regimens such as the immunomodulatory combination of lenalidomide and rituximab (R<sup>2</sup>) remains unexplored.

The aim of this ancillary analysis from the RELEVANCE trial (ClinicalTrials.gov identifier: NCT01476787 and NCT01650701) was to determine the prognostic value of baseline PET parameters, especially TMTV in patients with advanced stage FL requiring treatment, who received R<sup>2</sup> or R-chemo followed by rituximab maintenance, and its added value to existing clinical prognostic models.

## Methods

### Study design and participants

A PET ad-hoc analysis from the multicenter, international, phase 3 RELEVANCE trial was performed. Details of the RELEVANCE study design have been published previously<sup>14</sup>. Briefly, previously untreated patients with advanced disease (stage III/IV, or stage II with largest tumor diameter  $\geq 7$  cm) grades 1–3a follicular lymphoma requiring therapy were randomly assigned 1:1 to receive R<sup>2</sup> or R-chemo (investigator's choice between rituximab - cyclophosphamide, doxorubicin, vincristine, and prednisone, rituximab - bendamustine, or rituximab - cyclophosphamide, vincristine, and prednisone), followed by maintenance rituximab. PET/CT exams were optional, both at baseline and at the end of induction.

Thus, only those patients whose TMTV could be computed from a baseline PET scan were eligible for this study. Ethics approval was obtained for the RELEVANCE trial, registered at ClinicalTrials.gov (NCT01476787 and NCT01650701) and all participants provided written informed consent.

### Procedures

Baseline PET image data, in anonymized Digital Imaging and Communications in Medicine (DICOM) format, was collected for functional parameter measurements. All PET centers followed the current EANM guidelines for PET imaging of tumors<sup>15</sup>. Quality control rejected scans in which PET or CT was performed in several parts with burning errors in DICOM retrieval. PET/CT images were centrally reviewed by one expert nuclear physician (MM) blinded to patient outcome and analyzed using the free open-source software, Beth Israel Plugin for Fiji (<http://petctviewer.org>). The highest 18F-FDG uptake in lymphoma lesions was regarded as the SUVmax of the patient. The baseline TMTV was computed using the 41% SUVmax cut-off method after manual delineation of each lesion<sup>15, 16</sup>. The largest distance between the two furthest apart lesions, Dmax, was calculated in each patient and normalized to patient body surface area (BSA), yielding the standardized Dmax (SDmax).

### Statistical analysis

PFS was assessed by an independent review committee (IRC) and defined from the date of random assignment to the date of first documented relapse, progressive disease, death from any cause or the date of last contact. OS was calculated from the date of randomization until the



date of death from any cause or the date of last contact. Early event (POD24) was defined as relapse, progression, transformation, or death related to active lymphoma within 24 months after the date of random assignment<sup>17</sup>.

Survival functions were calculated using Kaplan-Meier estimates and comparison between categories was made with the log-rank test. For survival prediction, Xtile optimal cut-offs were found for PET parameters and for TMTV the previously published<sup>4</sup> cut-off of 510 cm<sup>3</sup> was also assessed. Univariate and multivariable analyses were performed using Cox proportional hazards models. Significant effects at level=0.05 in univariate analyses were included in a multivariate selection model: STEPWISE (significance level entry=0.2, significance level stay=0.10). Characteristics of populations were compared by using Fisher's exact test or  $\chi^2$  test for discrete variables and t test or Mann-Whitney test for continuous variables. To compare model performances, we used the C-index and the Akaike Criterion (AIC). Differences between results of comparative tests were significant if the two-sided p value was  $\leq 0.05$ . Statistical analyses used SAS 9.3 software (Yale University, New Haven, CT)<sup>27</sup>.

## Results

### Population

Clinical baseline characteristics of the patients with evaluable PET metrics (196 in the R2 arm and 210 in the R chemo arm) were similar to the overall trial population. Age, Ann Arbor stage, bone marrow infiltration, LDH, beta 2 microglobulin and FLIPI (Supplemental 1), were well balanced between the two treatment arms (Table 1) with no significant difference in the number of PFS, POD24 and OS events ( $p=0.87$ ,  $p=0.54$  and  $p=0.07$  respectively). In the R-chemo arm, 167/210 (80.7%) received R-CHOP and 31/210 (15.0%) received R-Bendamustine. With a median follow-up of 6.5 years (95% CI 6.4-6.8) for the PET population, the 6-y PFS was 57.8% and the 6y-OS was 90.9% with no significant difference between the two treatment arms ( $p=0.919$  and  $p=0.494$ ). A total of 160 PFS events occurred: 144 relapses and 16 deaths unrelated to FL. There were 37 deaths overall (including the 16 deaths without FL relapse). POD24 events occurred in 53 patients.

### Baseline PET parameters

PET baseline parameters were similar in patients in each randomization arm (Table 1). Median baseline TMTV was 284 cm<sup>3</sup>, median SUVmax 11.28 and median SDmax 0.32 m<sup>-1</sup>.

In univariate analysis, high SDmax (>0.29 m<sup>-1</sup>) was not associated with either PFS, POD24 or OS (p=0.12, p=0.42 and p=0.79 respectively). A high SUVmax (>19) was significantly associated with POD24 (p=0.026) and a trend towards a lower PFS was observed (p=0.08) Table 2. A high TMTV, defined using both the Xtile PFS cut-off of 431 cm<sup>3</sup> or the previously published cut-off of 510 cm<sup>3</sup>, was significantly associated with an inferior PFS (p=0.0018 and p=0.012 respectively) and POD 24 (p<0.001 and p=0.0014, Table 2) but not for OS (p=0.13 and p=0.25). Then, the previously published cut-off value of 510 cm<sup>3</sup> was selected to conduct subsequent analyses. Patients with a high TMTV (n=111, 27%) had a 6-year PFS of 47% vs 61.8% for those with a low TMTV (Figure 1A) (Figure 1B). Progression after 24 months was observed for 21.6% of the high TMTV patients versus 9.8% in the low TMTV group. In contrast, bulk as measured on the CT scan (either >6 cm or >7 cm) was not prognostic of PFS (p=0.978 and p=0.661 respectively). Patients with high TMTV had higher Ann Arbor stage (p<0.001), more extra nodal sites (p<0.001), more frequently elevated beta 2 microglobulin (p<0.001), higher FLIPI (p=0.002) and FLIPI2 scores (p<0.001).

#### Combination of TMTV with FLIPI

In multivariable analysis testing TMTV (> 510 cm<sup>3</sup>) with FLIPI (3-5), both factors remained independently associated with PFS (p=0.0119 and p=0.0379, respectively). Model performance was the highest for FLIPI+TMTV versus FLIPI alone versus TMTV alone to predict PFS. Similarly, for POD 24, the highest C-index and lowest AIC were found for the model combining both FLIPI and TMTV (Table 3).

The combination of FLIPI and TMTV stratified the overall population into 3 risk groups (Figure 2) : patients with no risk factors had a 6y-PFS of 67.7% (n=162, 40% reference), declining to 54.5% for patients with 1 risk factor (n=180, 44%; HR=1.45 ;[1.01-2.06], p=0.042) and 41.0% (n=64, 16%; HR=2.15 [1.39-3.31], p<0.001) for patients with both factors.

#### Prognostic impact of TMTV and FLIPI according to randomization arm

No significant interaction between treatment arms and TMTV or FLIPI were observed for PFS ( $p=0.31$  and  $p=0.60$ ) and POD 24 ( $p=0.10$  and  $p=0.89$ ).

The PFS of high TMTV patients was similar between the two treatment arms with a 6 year PFS of 45.1% (95% CI 30.9-58.2) in the R-chemo arm versus 49% (95% CI 33.1-63.1) in the R<sup>2</sup> arm (Figure 3B), as well as for low TMTV patients (Figure 3A). The median PFS was 68.6 months in the R chemo arm versus 71.4 months in R2 arm.

Considering each arm individually, a high TMTV remained significant to predict PFS in the R chemo arm ( $p=0.0093$ ) but not in the R2 arm ( $p=0.696$ ), although given the limited statistical power due to the small sample sizes, these results have to be taken with caution.

Similarly, the ultra-high risk group (high TMTV combined with FLIPI 3-5) had similar 6 years PFS whatever the treatment arms : 49.1 % (29.5-66.1 in the R<sup>2</sup> arm ; 29 patients) versus 33.3% (15.2-52.6) in the R-chemo arm (35 patients)). The median PFS was 45.3 months in the R chemo arm versus 60 months in R2 arm. Because of the low number of ultra-high risk patients, the confidence intervals are large and these results have to be read with caution.

## Discussion

This study confirmed the strong predictive value of TMTV in a large cohort of 406 patients with advanced stage FL as previously charted in smallest or retrospective series <sup>4, 10, 11</sup>. A high baseline TMTV  $>510$  cm<sup>3</sup> appears predictive of progression within the first two years of first line therapy and performed better than-FLIPI 2 in this regard. TMTV and FLIPI score were independent biomarkers and combining these two biomarkers identified a subgroup of patients (16%) at high risk of relapse with a 6-y PFS of 41%.

Currently, predicting outcomes at diagnosis for the individual patient with FL poses a major challenge. Median overall survival expectations beyond 20 years contrast with a significant minority (~20%) who experience early progression or histological transformation after treatment with a poor outcome. Many prognostic indices <sup>18</sup> or biomarkers <sup>19-21</sup> have been proposed in recent years to better identify a population at greatest risk for lymphoma-related death. At the same time, the prognostic value of TMTV has been suggested, in series including patients receiving anti-body-chemotherapy whom, for the most part, have not received maintenance antibody therapy <sup>4, 10, 11</sup>, a common practice (pre COVID) due to its PFS benefit<sup>22</sup>.

The current study demonstrates that TMTV remains strongly predictive of outcome in high tumor burden FL treated with R-chemo followed by antibody maintenance therapy. The RELEVANCE trial showed similar efficacy results of rituximab plus lenalidomide or rituximab plus chemotherapy both regimens followed by rituximab maintenance therapy<sup>14, 17</sup>. Interestingly this remains true even for high risk patients identified with high TMTV, FLIPI 3-5 or both adverse factors combined. However, the association between high TMTV and a lower PFS observed for the whole population was not found in patients treated with R2. Similarly, in the whole trial, R2 efficacy appeared to be more independent of conventional prognostic factors. Yet, given the limited statistical power due to the small sample sizes, this is only a trend and not a definite finding. In the Gallium trial, the prognostic role of TMTV appeared weaker<sup>12, 13</sup>, but patients received mostly Bendamustine whereas in RELEVANCE, the R chemo regimen was mainly (80.7%) R-CHOP. By contrast, in a retrospective study of 132 patients<sup>23</sup> receiving maintenance antibody therapy after a R chemo regimen for 89% of the patients (93% RCHOP, 6% RCVP), Rossi et al. did not find a significant PFS impact of high TMTV. However, this cohort included more elderly patients with nearly 80% > 60 years old contrasting with only half of the patients in the current study.

Using the same TMTV calculation method, we found similar median TMTV values to those obtained in the FOLLCOLL study<sup>4</sup>: 284 cm<sup>3</sup> (Q1-Q3; 144-553) versus 297 cm<sup>3</sup> (Q1-Q3; 135-567 cm<sup>3</sup>) respectively, confirming TMTV reproducibility and the possibility of using the same cut-off to dichotomize the population. Li et al.<sup>11</sup> identified a higher optimal threshold of 409 cm<sup>3</sup> to select the high risk group, in a study population in which 17% of patients had early stage FL (versus < 8% for the other two studies).

The predictive role of SUVmax is debated in FL. In retrospective series, a high SUVmax with a cut-off ranging from 12 to 18 was associated with the occurrence of POD24<sup>24</sup> or with a lower PFS<sup>23,25</sup> but large data from the GALLIUM study did not confirm the prognostic value of SUVmax on PFS<sup>12</sup>. Consistent with GALLIUM, in this prospective series, SUVmax was not predictive of PFS in either treatment arm although we observed a significant association with POD 24 in the R<sup>2</sup> population.

As a novel PET metric for characterizing lymphoma disease, the distance between two lesions that are the furthest apart ( $D_{max}$ ) has been proposed firstly in DLBCL<sup>26, 27</sup> and then applied in patients with HL<sup>28</sup>. This parameter, defining tumor dissemination, was complementary to TMTV for baseline risk stratification in these histologies (or lymphoma types). Recently, in FL, Li et al<sup>11</sup> observed that  $D_{max}$  was strongly predictive of PFS in a retrospective series of 126

patients, with 83% having advanced stage FL. They found an optimal cut-off of 57 cm, similar to that used in DLBCL<sup>26</sup>. By contrast, in our series of high tumor burden FL, we did not find a prognostic significance of either SD<sub>max</sub> or  $D_{max}$ . This discrepancy may be explained by the use of maintenance therapy, mandatory in RELEVANCE but not administered in the Li study.

In conclusion, the combination of TMTV with FLIPI identified a specific subgroup of patients with a heightened risk of relapse who might benefit from novel front-line approaches. TMTV might facilitate an individualized therapeutic approach in patients with high tumor FL by identification of those individuals more likely to relapse early after first line induction followed by antibody maintenance.

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ASC, LR, JT, IB, MM and FM conceived and designed the study; ASC, JT, PF, LN, EB, I W F, CH, LY, NB, HT, OC, RR, CP, IB, MM and FM collected and assembled the data;

ASC, LR, JT, RR, CP, IB, MM and FM analyzed and interpreted the data; and all authors contributed to writing the manuscript and approved the final version.

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Honoraria: Roche/Genentech, Takeda, Gilead Sciences, Bristol Myers Squibb, Merck, AbbVie, Celgene, Janssen, Amgen

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Expert Testimony: Roche/Genentech

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## Figure legends

### Figure 1

PFS and OS according to baseline TMTV with a cut-off of 510 cm<sup>3</sup> in the whole PET cohort.

### Figure 2

PFS and OS according to baseline TMTV with a cut-off of 510 cm<sup>3</sup> combined with FLIPI score, in the whole PET cohort.

### Figure 3

PFS according to treatment arms in low TMTV patients (A) and high TMTV (B).

