American Society of Hematology
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Axicabtagene ciloleucel versus standard of care in second-line large B-cell lymphoma: outcomes by metabolic tumor volume

Tracking no: BLD-2023-021620R2

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Abstract:
Metabolic tumor volume (MTV) assessed using 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography, a measure of tumor burden, is a promising prognostic indicator in large B-cell lymphoma (LBCL). This exploratory analysis evaluated relationships between baseline MTV (categorized as low [{less than or equal to}median] vs high [>median]) and clinical outcomes in the phase 3 ZUMA-7 study (NCT03391466). Patients with LBCL relapsed within 12 months of or refractory to first-line chemoimmunotherapy were randomized 1:1 to axicabtagene ciloleucel (axi-cel; autologous anti-CD19 chimeric antigen receptor [CAR] T-cell therapy) or standard care (2-3 cycles of chemoimmunotherapy followed by high-dose chemotherapy with autologous stem-cell transplantation in patients who had a response). All P values are descriptive. Within high and low MTV subgroups, event-free survival (EFS) and progression-free survival (PFS) were superior with axi-cel vs standard care (all HR {less than or equal to}0.523; P<.01). EFS in patients with high MTV (vs low MTV) was numerically shorter with axi-cel (HR, 1.448; P=.06) and was significantly shorter with standard care (HR, 1.486; P=.02). PFS was shorter in patients with high MTV vs low MTV in both the axi-cel (HR,1.660; P=.02) and standard-care (HR, 1.635; P=.02) arms, and median MTV was lower in patients in ongoing response at data cutoff vs others (both P{less than or equal to}.01). Median MTV was higher in axi-cel-treated patients who experienced grade {greater than or equal to}3 neurologic events or cytokine release syndrome (CRS) than in patients with grade 1/2 or no neurologic events or CRS, respectively (both P{less than or equal to}.03). Baseline MTV {less than or equal to}median was associated with better clinical outcomes in patients receiving axi-cel or standard care for second-line LBCL.

Conflict of interest: COI declared - see note

COI notes: FLL: consulting/advisory role for Allogene, Amgen, bluebird bio, Bristol Myers Squibb, Celgene, Calibr, Cellular Biomedicine Group, Cowen, ecoR1, Emerging Therapy Solutions Gerson Lehman Group, GammaDelta Therapeutics, Iovance, Janssen, Kite, a Gilead Company, Legend Biotech, Novartis, Umoja Biopharma, and Wugen; research funding from Allogene, Kite, and Novartis; and patents, royalties, other intellectual property from several patents held by the institution in my name (unlicensed) in the field of cellular immunotherapy. OOO: research funding from Kite, a Gilead Company, and consulting/advisory role for Janssen, Pfizer, Novartis, Curio Science, ADC Therapeutics, and TG Therapeutics. JK: honoraria from Amgen, AstraZeneca, Bristol Myers Squibb, Celgene, Gilead, Janssen, Karyopharm, Merck, Novartis, Roche, and Seagen; consulting/advisory role for AbbVie, Bristol Myers Squibb, Gilead, Karyopharm, Merck, Roche, and Seagen; and research funding from Roche and Janssen. C Th: honoraria from and consulting/advisory role for AbbVie, Bristol Myers Squibb, Celgene, Incyte, Kite, a Gilead Company, Novartis, Roche, and Takeda; and travel support from Bristol Myers Squibb, Celgene, Kite, Novartis, Roche, and Takeda. FM: consulting/advisory role for AbbVie, Bristol Myers Squibb, Epizyme, Genmab, Gilead Sciences, Novartis, and Roche; speakers' bureau participation for Roche; and expert testimony for Roche and Genentech. GS: honoraria from AbbVie, Amgen, Bayer, Epizyme, Regeneron, Roche, MorphoSys, Kite, a Gilead Company/Gilead, and Novartis; consultancy/advisory role for Bristol Myers Squibb, Celgene, Incyte, Ipsen, Janssen, Kite, Loxo, Miltenyi, MorphoSys, Novartis, and Rapt; participation on a data safety monitoring board or advisory board for AbbVie, BeiGene, Bristol Myers Squibb, Celgene, Debiopharm, Epizyme, Genentech/Roche, Genmab, Incyte, Kite, Miltenyi, MorphoSys, Takeda, and VelosBio. SPR: employment with, stock, or other ownership in and patents, royalties, other intellectual property from Precision Molecular, Inc and PlenaryAI, Inc; honoraria from, speakers' bureau participation for, and travel support from Lantheus Pharmaceuticals, Inc; consultancy/advisory role for and research funding from Precision Molecular, Inc, Lantheus Pharmaceuticals, Inc, and PlenaryAI, Inc. SV: employment with and research funding from Kite, a Gilead Company, and stock or other ownership in Gilead. JW: employment with and research funding from Kite, a Gilead Company, and stock or other ownership in Gilead. SF: employment and stock or ownership with Kite, a Gilead Company, and patents, royalties, and other intellectual property from Tusk Therapeutics. C To: employment with Kite, a Gilead Company, and stock or other ownership in Gilead Sciences. PC: employment with Kite, a Gilead Company; stock or other ownership in Gilead Sciences; and travel support from Kite. MS: employment with, honoraria from, travel support from, and other relationships with Kite, a Gilead Company; and stock or other ownership in Gilead Sciences. RK: employment with Imaging Endpoints; stock or other ownership with Teladoc, Televiev, Globavir, Verve, Renibus; consulting or advisory role for Dynamicure, Fore Biotherapeutics, SonALAsense, Dracen, Day One, and FibroGen; patents, royalties, and other intellectual property with Imaging Endpoints. MJK: honoraria from and consulting/advisory role for Bristol Myers Squibb, Celgene, Kite, a Gilead Company, Miltenyi Biotech, Novartis, and Roche; research funding from Kite, Roche, Takeda, and Celgene; and travel support from Kite, Miltenyi Biotech, Novartis, and Roche.

Preprint server: No;

Author contributions and disclosures: F.L.L., S.F., C.To., P.C., M.S., and R.K. designed the study. F.L.L., O.O.O., J.K., C.Th., F.M., G.S., S.P.R., S.V., J.W., R.K., and M.J.K. enrolled and treated patients, and collected data. All authors participated in analyzing and interpreting the data, writing the manuscript, and approving the final submitted version.

Non-author contributions and disclosures: Yes; We thank the patients who participated in this study and their families, caregivers, and friends; the study investigators, coordinators, and healthcare staff at each site; Melinda Ramsey, PhD, of Nexus Global Group Science, for medical writing assistance, with funding provided by Kite; and all employees of Kite involved over the course of the study for their contributions. F.L.L. is a Clinical Scholar of the Leukemia and Lymphoma Society.

Agreement to Share Publication-Related Data and Data Sharing Statement: Kite is committed to sharing clinical trial data with external medical experts and scientific researchers in the interest of advancing public health, and access can be requested by contacting medinfo@kitepharma.com.

Clinical trial registration information (if any): Clinicaltrials.gov NCT03391466

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Data Sharing Statement

Kite is committed to sharing clinical trial data with external medical experts and scientific researchers in the interest of advancing public health, and access can be requested by contacting medinfo@kitepharma.com.

Article type: Regular Article

Text word count: 3903/4000

Abstract word count: 250/250

Tables/Figures: 6/7

Scientific Categories: Clinical trials and observations (primary); immunobiology and immunotherapy (secondary)

Key Points

- MTV impacted outcomes to second-line treatment in both arms, and axi-cel improved EFS and PFS over standard care, irrespective of MTV
- Baseline MTV associated with grade ≥3 CRS and neurologic events following axi-cel treatment

Abstract

Metabolic tumor volume (MTV) assessed using 2-deoxy-2-[^{18}F]fluoro-D-glucose positron emission tomography, a measure of tumor burden, is a promising prognostic indicator in large B-cell lymphoma (LBCL). This exploratory analysis evaluated relationships between baseline MTV (categorized as low [≤median] vs high [>median]) and clinical outcomes in the phase 3 ZUMA-7 study (NCT03391466). Patients with LBCL relapsed within 12 months of or refractory to first-line chemoimmunotherapy were randomized 1:1 to axicabtagene ciloleucel (axi-cel; autologous anti-CD19 chimeric antigen receptor [CAR] T-cell therapy) or standard care (2-3 cycles of chemoimmunotherapy followed by high-dose chemotherapy with autologous stem-cell transplantation in patients who had a response). All *P* values are descriptive. Within high and low MTV subgroups, event-free survival (EFS) and progression-free survival (PFS) were superior with axi-cel vs standard care (all HR ≤0.523; *P*<.01). EFS in patients with high MTV (vs low MTV) was numerically shorter with axi-cel (HR, 1.448; *P*=.06) and was significantly shorter with standard care (HR, 1.486; *P*=.02). PFS was shorter in patients with high MTV vs low MTV in both the axi-cel (HR,1.660; *P*=.02) and standard-care (HR, 1.635; *P*=.02) arms, and median MTV was lower in patients in ongoing response at data cutoff vs others (both *P*≤.01). Median MTV was higher in axi-cel–treated patients who experienced grade ≥3 neurologic events or cytokine release syndrome (CRS) than in patients with grade 1/2 or no neurologic events or CRS, respectively (both *P*≤.03). Baseline MTV ≤median was associated with better clinical outcomes in patients receiving axi-cel or standard care for second-line LBCL.

Introduction

First-line chemoimmunotherapy for large B-cell lymphoma (LBCL) is curative in many patients, but approximately 40% experience disease progression or relapse, require new anti-lymphoma therapy, or die within 2 years in the post-rituximab era.[1] Until recently, second-line standard care was high-dose chemotherapy (HDT) with autologous stem-cell transplantation (ASCT) for those who respond to salvage chemoimmunotherapy.[2] However, based on results of the phase 3 ZUMA-7 and TRANSFORM studies, autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy may replace salvage chemoimmunotherapy and HDT/ASCT as standard of care for patients with LBCL who are refractory to first-line therapy or relapsed within 12 months.[3,4] In ZUMA-7, second-line therapy with axicabtagene ciloleucel (axi-cel) significantly prolonged event-free survival (EFS) vs standard care in patients with relapsed/refractory (R/R) LBCL (hazard ratio [HR], 0.398; stratified log-rank $P < .0001$).[5] The primary overall survival (OS) analysis of ZUMA-7 (median follow-up, 47.2 months) demonstrated a statistically significant improvement in OS with axi-cel over standard care. Median OS was not reached in the axi-cel arm and was 31.1 months in the standard-care arm, with 4-year OS rates of 54.6% and 46.0%, respectively (HR, 0.73; stratified log-rank $P < .03$).[6] Axi-cel was superior to standard care across negative prognostic subgroups, including patients with elevated lactate dehydrogenase (LDH) and those with high tumor burden (TB) determined by sum of the product of perpendicular diameters (SPD).[7]

High TB has long been recognized as an independent risk factor for poor outcome in LBCL[8] and other lymphomas.[9,10] TB measurement has evolved from assessing maximal tumor dimension using clinical examination, chest radiography, and lymphography to determining total tumor volume in nodal and extranodal sites by combining positron emission tomography (PET) and computed tomography (CT).[11] Still, there is no standard procedure for quantifying TB in lymphoma. Cheson et al[12] described the estimation of TB using SPD for up to 6 target measurable lesions on CT. Although SPD is widely used to evaluate TB in LBCL,[13] this CT-

based method does not account for nonmeasured lesions or metabolic activity. In [^{18}F]fluoro-D-glucose (FDG)-avid lymphomas, 2-deoxy-2-FDG PET-CT, which achieves precise anatomic localization of metabolically active tissues, is considered the gold standard for staging and response assessment[13-15] and has emerged as a basis for measuring TB.[11]

Tumor burden based on metabolic tumor volume (MTV) assessed using FDG PET-CT is a promising prognostic indicator in LBCL. Although there clearly is a need for standard methods for quantifying MTV across tumor and treatment types, higher pretreatment MTV has consistently predicted shorter progression-free survival (PFS) and OS in patients with LBCL receiving standard first-line chemoimmunotherapy[16-20] or platinum-based salvage chemotherapy.[21] Furthermore, higher pretreatment MTV was associated with poorer clinical outcomes in patients receiving anti-CD19 CAR T-cell therapy for R/R LBCL after 2 or more lines of therapy.[22-26] Here, we present exploratory analyses of relationships between whole-body MTV at baseline and clinical outcomes for patients treated with axi-cel or standard care in the ZUMA-7 study.

Methods

Patients

Full details on the ZUMA-7 study (NCT03391466) were previously reported.[5] Briefly, eligible patients were aged ≥18 years (with no upper age limit) and had LBCL confirmed by histology according to World Health Organization 2016 classification criteria.[27] Patients were refractory to adequate first-line treatment consisting of an anti-CD20 monoclonal antibody and anthracycline-containing regimen or had relapsed ≤12 months after completing first-line chemoimmunotherapy.

Study design

Patients were randomized 1:1 to axi-cel or investigator-selected standard chemoimmunotherapy, stratified by response to first-line therapy and second-line age-adjusted

International Prognostic Index.[5] Patients in the axi-cel arm received a single infusion of axi-cel (target dose 2×10^6 CAR T cells/kg) after undergoing leukapheresis followed by conditioning chemotherapy with cyclophosphamide (500 mg/m^2/day) and fludarabine (30 mg/m^2/day) 5, 4, and 3 days before axi-cel infusion. Bridging therapy was optional and limited to corticosteroids.[5] Patients randomized to standard care received 2 to 3 cycles of protocol-defined, investigator-selected platinum-based chemoimmunotherapy, and those who had a complete response (CR) or partial response (PR) proceeded to HDT-ASCT. Disease assessments per Lugano classification[13] occurred at time points specified from randomization. Although crossover between treatment groups was not planned, patients in either arm could receive off-protocol treatment, including cellular immunotherapy. The trial was conducted after institutional review board approval of the protocol and in compliance with the Declaration of Helsinki, and all patients provided written, informed consent.

Endpoints and assessments

The primary endpoint of the study was EFS, defined as the time from randomization to the earliest date of disease progression according to the Lugano classification,[13] new lymphoma therapy, death from any cause, or a best response of stable disease (SD) up to and including the response on Day 150 assessment after randomization, per blinded central review. Key secondary endpoints were objective response rate (ORR) and OS. Additional secondary endpoints were progression-free survival (PFS) and incidence and severity of adverse events.

Tumor burden based on SPD (per International Working Group 2007 criteria[12]) was assessed by the central imaging laboratory, as previously described.[5] MTV was based on attenuation-corrected, whole-body FDG PET-CT scans at screening. Although a standardized approach for quantification of MTV is lacking in the field, our procedures for MTV determination were carried out with a pre-defined and consistent methodology across patients, similar to that employed by others.[19,20,23,28] Briefly, whole-body FDG PET-CT scans were performed in ZUMA-7 patients who underwent at least a 4-hour fast before FDG administration. Patients with

acceptable blood glucose values (<200 mg/dl), received an intravenous dose of FDG (recommended range: 370–740 MBq [10 – 20 mCi] with weight-based adjustments allowed) per institutional standard procedures. Following a 60 (±10) minute incubation period, low-dose CT for attenuation correction (CTAC) was obtained (70–80mA, 120–140 kvP) followed by PET emission scanning in 2D or 3D mode at 2–5 minutes/bed position. Reconstruction algorithms (iterative reconstruction, with time of flight, if available) and postacquisition filtering were performed per manufacturer's recommendation based on local institutional practices. Images were uploaded to a centralized site to determine MTV. Whole-tumor volumes of interest (VOI) were placed on individual tumors using a predefined, semiautomated approach that included semiautomated placement of outlines around regions of abnormal FDG uptake at least moderately greater than that of normal liver (visual Lugano score >3) followed by manual adjustments of the lesion contours by a single PET radiologist per patient to ensure entire tumor lesions were included and/or nontumorous/normal tissue regions were excluded. Subsequent radiologist-defined adjustments of VOI placement included adding regions of tumor not initially captured and excluding normal tissue. MTV was calculated as the number of voxels, or volume picture elements, with standardized uptake value (SUV) measurements between 41% and 100% of tumor SUVmax (per European Association of Nuclear Medicine guidelines[29]) and reported as total MTV (mL) per patient. Low and high MTV were defined as MTV ≤median and >median, respectively. Associations between MTV and baseline characteristics and clinical outcomes were assessed. Safety analyses were limited to cytokine release syndrome (CRS) and neurologic events.

Total lesion glycolysis (TLG) was defined as the MTV x SUVmean for a given lesion. Total TLG is reported as the sum of all lesion TLG for a given patient. The International Metabolic Prognostic Index (IMPI) was also applied in ZUMA-7 patients with baseline data for MTV, age, and Ann Arbor stage.[30] For IMPI, patients were divided into 2 groups (low and high IMPI) of the same size as the age-adjusted International Prognostic Index (IPI) categories (0-1

and 2-3). For this purpose, patients were ranked by their absolute IMPI, and patient numbers were matched according with the number of the corresponding age-adjusted IPI categories. Associations between IMPI and EFS and PFS were evaluated to determine whether age and Ann Arbor stage would improve the predictive value of MTV.

Statistical analyses

ZUMA-7 primary efficacy and safety analyses were previously reported.[5] The analyses presented here were exploratory. Analyses evaluating relationships between MTV and efficacy outcomes were based on the full analysis set, whereas analyses of MTV and safety outcomes were based on the safety set. All *P* values are descriptive.

Baseline MTV data were summarized by treatment arm and were pooled for analysis of MTV by baseline characteristics: age (<65 vs ≥65 years), germinal center B cell like (GCB) vs non-GCB, prognostic subgroups (high-grade B-cell lymphoma [HGBL] vs non-HGBL), lactate dehydrogenase (LDH; elevated vs normal), primary refractory vs relapsed, CD19 positivity by immunohistochemistry (IHC; yes vs no), and CD19 H-score (by IHC; ≤median vs >median). Two-sided *P* values for each categorical comparison were calculated using the Wilcoxon rank sum test. Spearman correlation estimates and *P* values from a Fisher's *z* transformation were used to summarize relationships between baseline MTV and continuous baseline covariates (ie, SPD, LDH).

Kaplan–Meier estimates were provided for EFS and PFS. Estimated HRs, 95% CIs, and descriptive 2-sided P values were calculated from a Cox proportional-hazards model. For these analyses, patients were categorized into either high or low MTV. The same methods were used to evaluate associations between IMPI (high vs low based on median) and time-to-event outcomes.

Exploration of alternative MTV thresholds included evaluation of EFS and PFS by baseline MTV quartiles and by best MTV threshold. The best MTV threshold was based on log-rank statistics that resulted in the greatest separation (ie, lowest *P* value) between the high-MTV

and low-MTV curves for EFS and PFS within each arm (ie, 4 different thresholds). Additionally, an unstratified Cox regression model with the log2 of baseline MTV as a continuous variable was used to provide estimated HRs, 95% CIs, and *P* values for EFS and PFS in the axi-cel and standard-care arms.

Several analyses were also conducted to compare MTV to other measures of TB using the ZUMA-7 dataset. Spearman correlation estimates and *P* values from a Fisher's z transformation were used to evaluate relationships between baseline MTV and SUVmax or SPD, or TLG. Similar to the Kaplan-Meier methods described for MTV, EFS and PFS were evaluated for both arms based on high versus low SUVmax, SPD, and TLG, with median as the threshold for each measure.

We used multivariate analyses to determine the potential predictive value of MTV for time-to-event outcomes after adjustment for other prognostic factors (ie, age, LDH, and second-line age-adjusted IPI). An unstratified Cox regression model with baseline MTV (high vs low according to median or best threshold), derived second-line age-adjusted IPI (2-3 vs 0-1), baseline age group (≥65 y vs <65 y), and baseline LDH status (elevated vs normal) as covariates was used to provide estimated HRs, 2-sided 95% CIs, and *P* values.

The Wilcoxon rank sum test was used to compare baseline MTV within treatment arms for the following patient groups: responders (CR + PR) vs nonresponders (SD + progressive disease [PD]); CR vs others (PR + SD + PD); and ongoing response vs others (progression after response + nonresponder). Logistic regression was performed to assess the association between MTV and clinical outcome (eg, CR vs others) within the treatment arms. The Wilcoxon rank sum test was also used to compare MTV data for patients with neurologic events (grade ≥3 vs grades 2, 1, and none) and CRS (grade ≥3 vs grades 2, 1, and none).

The trial was conducted after institutional review board approval of the protocol

Results

Of 359 patients randomized in the ZUMA-7 study between January 25, 2018, and October 4, 2019 (full analysis set), 340 (axi-cel, n = 175; standard care, n = 165) were evaluable for MTV (ie, had baseline and 1 post-baseline scan available). The median follow-up from randomization to the data-cutoff date (March 18, 2021) for all randomized patients was 24.9 months. Median MTV at baseline was 231.07 mL (range, 0.04-16,669.3) overall, and was comparable in the axi-cel and standard-care arms (Table 1). Representative images of patients with high and low MTV are shown in Figure 1. Median MTV was significantly higher in patients aged <65 years vs ≥65 years and in patients with elevated vs normal LDH. MTV was moderately correlated with both SPD (Spearman correlation, 0.522; 95% CI, 0.436-0.599; Figure 2A) and LDH (Spearman correlation, 0.450; 95% CI, 0.361-0.531; Figure 2B).

EFS in the axi-cel arm was superior to standard care both in patients with high MTV (HR, 0.417; 95% CI, 0.293-0.592) and in patients with low MTV (HR, 0.421; 95% CI, 0.286-0.619; Figure 3A). Among axi-cel–treated patients, EFS was numerically shorter in those with high (vs low) MTV (HR, 1.448; 95% CI, 0.980-2.139). Similarly, EFS was shorter in standard care-treated patients with high (vs low) MTV (HR, 1.486; 95% CI, 1.055-2.093). PFS in the axi-cel arm was superior to standard care in patients with high MTV (HR, 0.523; 95% CI, 0.357-0.765) and low MTV (HR, 0.501; 95% CI, 0.324-0.773; Figure 3B). PFS was shorter in those with high (vs low) MTV in both the axi-cel (HR, 1.660; 95% CI, 1.097-2.513) and standard-care arms (HR, 1.635; 95% CI, 1.098-2.433).

A significant EFS benefit of axi-cel over standard care was maintained across quartiles of MTV (Supplemental Figure 1). Compared with the axi-cel group, the standard-care group demonstrated more pronounced EFS worsening from MTV quartile 2 to MTV quartile 4 (Supplemental Figure 1). Best-threshold analysis confirmed that MTV was associated with EFS and PFS in both the axi-cel (Supplemental Figure 2A, C) and standard-care (Supplemental

Figure 2B, D) arms (all $P \leq .01$). Consistent with these findings, the continuous variable analysis demonstrated that one unit increase in MTV on a log2 scale (equivalent to doubling of MTV on a raw scale) resulted in a 10% increase in risk for EFS events in the axi-cel arm ($P = .02$) and a 14% increase in the standard-care arm ($P = .01$). Similar trends were observed for PFS (Supplemental Table 1).

Associations observed between IMPI, which combines MTV, age, and Ann Arbor stage, and both EFS and PFS (Supplemental Figure 3) were similar to those observed with MTV alone and time-to-event outcomes. Baseline MTV moderately correlated with baseline SUVmax, and SPD, while a very strong correlation was observed between MTV and TLG (Supplemental Table 2). Comparison of descriptive *P* values suggested that MTV was a better predictor of EFS than SUVmax, SPD, or TLG in the axi-cel arm, and outperformed SUVmax and TLG in the standard care arm (Supplemental Table 3). MTV was a better predictor of PFS than SUVmax or SPD in both the axi-cel and standard-care arms (Supplemental Table 3), while MTV was comparable to TLG for prediction of PFS. Furthermore, within high and low groups defined by median SUVmax (Supplemental Figure 4) SPD (Supplemental Figure 5), or TLG (Supplemental Figure 6), axi-cel consistently prolonged EFS and PFS over standard care.

In the multivariate analysis, when high and low MTV were based on the median, *P* values for EFS and PFS did not reach significance by descriptive statistics. However, comparison of *P* values suggested that, in both arms, MTV was more predictive of EFS than second-line age-adjusted IPI, age, and LDH when adjusted for the other 3 factors. MTV was also more predictive for PFS than the other factors in the axi-cel arm (Supplemental Table 4). When multivariate analysis was repeated with high and low MTV based on best threshold, MTV was significantly predictive of EFS and PFS after adjustment for second-line age-adjusted IPI, age, and LDH. After adjustment of each individual covariate for the remaining 3, only MTV had significant impact on EFS and PFS in the axi-cel and standard-care arms (Supplemental Table 5).

Median MTV was similar between axi-cel responders (228.66 mL; range, 2.3-16,669.3) and nonresponders (233.11 mL; range, 6.8-6823.5; Figure 4A). The difference in median MTV between standard-care responders and nonresponders also did not meet statistical significance (219.32 mL; [range, 0.04-2811.2] vs 320.34 mL [range, 10.8-2593.9]). In both the axi-cel and standard-care arms, median MTV was lower in patients who were in ongoing response at data cutoff compared with others (axi-cel: 163.05 mL [range, 2.3-5317.7] vs 322.82 mL [6.8-16,669.3]; standard care: 139.48 mL [range, 0.04-760.2] vs 305.98 mL [range, 10.8-2593.9]; Figure 4B). Median MTV was also lower among patients with CR compared with patients not in CR receiving axi-cel (199.95 mL [range, 2.3-13,527.0] vs 322.82 mL [range, 6.8-16,669.3]; *P* = .02) or standard care (192.86 mL [range, 0.04-1354.7] vs 296.24 mL [range, 3.6-2811.2]; *P* = .01; Supplemental Figure 7). Consistently, logistic regression analyses demonstrated significant negative associations between CR rate and baseline MTV in the axi-cel (*P* = .01; Supplemental Figure 8A) and standard care (*P* = .02; Supplemental Figure 8B) arms.

The safety set included 338 patients. Among axi-cel–treated patients, median MTV was higher for patients who experienced grade ≥3 neurologic events vs patients who experienced grade 1/2 or no neurologic events (320.93 mL [range, 24.3-13,527.0] vs 195.46 mL [range, 2.3-16,669.3]; Figure 5A). Median MTV was also higher for axi-cel–treated patients who experienced grade ≥3 CRS compared with patients who experienced grade 1/2 or no CRS (582.93 mL [range, 114.6-2508.6] vs 205.73 mL [range, 2.3-16,669.3]; Figure 5B). In the standard-care arm, no association between MTV and neurologic events was observed, and no CRS was reported.

Except for modest correlations with baseline and peak interleukin-7 levels, baseline MTV did not associate with pharmacokinetic, pharmacodynamic, or product parameters. In the axi-cel arm, neither CAR T-cell peak nor $AUC_{0\text{-}28}$ was significantly associated with ongoing response, even when adjusted for MTV (ratio between CAR T-cell peak or $AUC_{0\text{-}28}$ and MTV; Supplemental Figure 9), indicating that the extent of in vivo CAR T-cell expansion was not a

strong limiting factor for durable responses (vs others) across the range of MTV in the ZUMA-7 study.

Discussion

This analysis is the first to evaluate MTV in a large, randomized study of patients with R/R LBCL. Similar to the ZUMA-7 primary analysis and results in subgroups defined by SPD, LDH, and other established prognostic factors,[5,7] the EFS benefit of axi-cel vs standard care was maintained in both high- and low-MTV subgroups. Higher MTV was associated with shorter EFS, shorter PFS, and a reduced likelihood of ongoing response in both arms, and more severe neurologic events and CRS in axi-cel—treated patients. These findings confirm previous observations of worse outcomes in patients with high vs low baseline TB for both CAR T-cell therapy and standard care. However, the strength of relationships between TB and efficacy of CAR T-cell therapy differs across patient populations and methods used to quantify TB.[31] In multivariate analyses of data from the ZUMA-1 study, baseline TB measured by SPD was negatively correlated with probability of durable response in patients with R/R LBCL treated with axi-cel in third or later lines.[32] Univariate analyses revealed a significant association between SPD and probability of grade ≥3 neurologic events, but not grade ≥3 CRS.[32] In ZUMA-7, high TB measured via SPD (>median) was predictive of poorer EFS in the standard-care arm (HR, 1.5; $P < .02$), but not in the axi-cel arm (HR, 0.95; $P = .68$).[7] Thus, compared with SPD, MTV is a better predictor of outcomes with second-line therapy in patients with R/R LBCL. MTV also outperformed both SUVmax and TLG with respect to prediction of EFS in both arms of ZUMA-7.

Tumor burden defined by SPD takes into account the dimensions of only 6 target, measurable lesions on CT[12] and thus is not a comprehensive reflection of total tumor load. Because CT scans lack functional information, osseous and bone marrow lesions and those located within normal-sized organs may not be detected. FDG PET is a whole-body imaging

method with the sensitivity to detect metabolic changes in involved areas before structural changes are visible.[33] Thus, MTV based on FDG PET-CT is a more sensitive and accurate measure of TB than SPD and, for that reason, may be a better prognostic marker.

Standardization of MTV quantification (eg, software package, SUV threshold, manual intervention to delimit tumors from adjacent sites of physiological uptake), application, and interpretation are needed to improve clinical utility and facilitate cross-study comparisons.[11] It should be noted that the range of MTV differs between datasets, different methodologies may yield different MTV values for the same patient, and MTV may differentially associate with the outcomes of one treatment versus another. Thus, our results only apply to the ZUMA-7 dataset. Establishment of an absolute threshold for delineating high versus low MTV in routine practice was not our objective and may not be feasible.

Several groups have demonstrated that the addition of other baseline factors improves the prognostic potential of MTV for survival outcomes in LBCL.[34,35] Mikhaeel et al[30] introduced the IMPI based on the finding that adding age and Ann Arbor stage (a measure of disease dissemination) to MTV improved the prediction of PFS and OS in patients with LBCL receiving first-line chemoimmunotherapy. In this analysis, the IMPI outperformed the conventional IPI in predicting PFS and OS.[30] In patients receiving CAR T-cell therapy for later-line R/R LBCL, IMPI was a better predictive factor than IPI for PFS, but neither score significantly associated with ORR, duration of response, or OS.[36] Although the predictive value of the IMPI (high vs low) was similar to MTV alone in ZUMA-7 patients treated with axi-cel or standard care, findings to date support MTV as a better reflection of disease burden and biology than the surrogate measures included in the IPI (ie, LDH and extranodal involvement).[30,36] The results of our multivariate analyses also support the predictive value of MTV beyond that provided by other prognostic indices, including second-line age-adjusted IPI.

Unlike CT, FDG PET-CT–based methods allow discrimination of viable tumors from necrotic/fibrotic lesions, which is particularly beneficial during interim and post-treatment

assessment.[33] Although our analyses focused on the predictive value of baseline MTV for clinical outcomes in R/R LBCL, several groups have shown value of MTV assessment at early post-infusion timepoints.[26,37,38] For example, Hong et al[38] identified high MTV 1 month after CAR T-cell infusion as a significant risk factor for poor PFS among 41 patients with R/R LBCL receiving CAR T-cell therapy in the third or later line. Future analyses of amenable data from axi-cel studies may assess the predictive potential of MTV at post-infusion timepoints.

The current analysis is limited because it was not prespecified and therefore not statistically powered for definitive conclusions. Furthermore, alternative methods of MTV determination and alternative analyses that incorporate morphology, intensity, or special distribution of lesions, and/or a different threshold for categorizing high vs low MTV might have yielded different results when applied to the ZUMA-7 dataset. For example, a more time-consuming manual approach to MTV determination may provide more accuracy regarding tumor burden.[22,39]

Despite the lack of a global, standardized approach to MTV quantification (which was beyond the scope of this investigation), our median, quartile, best-threshold, continuous-variable, and multivariate analyses all support MTV as biologically and clinically relevant. Finally, baseline MTV was determined at screening in ZUMA-7, before optional bridging therapy with corticosteroids during axi-cel manufacturing. The impact of bridging, reported for 36% of the axi-cel arm, on relationships between MTV and clinical outcomes in ZUMA-7 patients receiving axi-cel was not determined.

In conclusion, in the first analysis of the relationship between MTV and clinical outcome in a large, randomized study of CAR T-cell therapy in R/R LBCL, axi-cel demonstrated superiority over standard care for both high and low MTV groups. For both arms, however, baseline MTV differentiated patients with R/R LBCL who experienced more vs less benefit from second-line therapy. MTV was also positively associated with severity of CAR T-cell-related toxicities. Although standardization of MTV assessment is needed to facilitate broader clinical

use, using high MTV to identify poor-risk patients has the potential to inform treatment planning and monitoring and may prompt earlier changes in therapy.

Acknowledgement

We thank the patients who participated in this study and their families, caregivers, and friends; the study investigators, coordinators, and healthcare staff at each site; Melinda Ramsey, PhD, of Nexus Global Group Science, for medical writing assistance, with funding provided by Kite; and all employees of Kite involved over the course of the study for their contributions. F.L.L. is a Clinical Scholar of the Leukemia and Lymphoma Society.

Authorship Contributions

F.L.L., S.F., C.To., P.C., M.S., and R.K. designed the study. F.L.L., O.O.O., J.K., C.Th., F.M., G.S., S.P.R., S.V., J.W., R.K., and M.J.K. enrolled and treated patients, and collected data. All authors participated in analyzing and interpreting the data, writing the manuscript, and approving the final submitted version.

Disclosure of Conflicts of Interest

FLL: consulting/advisory role for Allogene, Amgen, bluebird bio, Bristol Myers Squibb, Celgene, Calibr, Cellular Biomedicine Group, Cowen, ecoR1, Emerging Therapy Solutions Gerson Lehman Group, GammaDelta Therapeutics, Iovance, Janssen, Kite, a Gilead Company, Legend Biotech, Novartis, Umoja Biopharma, and Wugen; research funding from Allogene, Kite, and Novartis; and patents, royalties, other intellectual property from several patents held by the institution in my name (unlicensed) in the field of cellular immunotherapy. **OOO:** research funding from Kite, a Gilead Company, and consulting/advisory role for Janssen, Pfizer, Novartis, Curio Science, ADC Therapeutics, and TG Therapeutics. **JK:** honoraria from Amgen, AstraZeneca, Bristol Myers Squibb, Celgene, Gilead, Janssen, Karyopharm, Merck, Novartis,

Roche, and Seagen; consulting/advisory role for AbbVie, Bristol Myers Squibb, Gilead, Karyopharm, Merck, Roche, and Seagen; and research funding from Roche and Janssen. **C Th:** honoraria from and consulting/advisory role for AbbVie, Bristol Myers Squibb, Celgene, Incyte, Kite, a Gilead Company, Novartis, Roche, and Takeda; and travel support from Bristol Myers Squibb, Celgene, Kite, Novartis, Roche, and Takeda. **FM:** consulting/advisory role for AbbVie, Bristol Myers Squibb, Epizyme, Genmab, Gilead Sciences, Novartis, and Roche; speakers' bureau participation for Roche; and expert testimony for Roche and Genentech. **GS:** honoraria from AbbVie, Amgen, Bayer, Epizyme, Regeneron, Roche, MorphoSys, Kite, a Gilead Company/Gilead, and Novartis; consultancy/advisory role for Bristol Myers Squibb, Celgene, Incyte, Ipsen, Janssen, Kite, Loxo, Miltenyi, MorphoSys, Novartis, and Rapt; participation on a data safety monitoring board or advisory board for AbbVie, BeiGene, Bristol Myers Squibb, Celgene, Debiopharm, Epizyme, Genentech/Roche, Genmab, Incyte, Kite, Miltenyi, MorphoSys, Takeda, and VelosBio. **SPR:** employment with, stock, or other ownership in and patents, royalties, other intellectual property from Precision Molecular, Inc and PlenaryAI, Inc; honoraria from, speakers' bureau participation for, and travel support from Lantheus Pharmaceuticals, Inc; consultancy/advisory role for and research funding from Precision Molecular, Inc, Lantheus Pharmaceuticals, Inc, and PlenaryAI, Inc. **SV:** employment with and research funding from Kite, a Gilead Company, and stock or other ownership in Gilead. **JW:** employment with and research funding from Kite, a Gilead Company, and stock or other ownership in Gilead. **SF:** employment and stock or ownership with Kite, a Gilead Company, and patents, royalties, and other intellectual property from Tusk Therapeutics. **C To:** employment with Kite, a Gilead Company, and stock or other ownership in Gilead Sciences. **PC:** employment with Kite, a Gilead Company; stock or other ownership in Gilead Sciences; and travel support from Kite. **MS:** employment with, honoraria from, travel support from, and other relationships with Kite, a Gilead Company; and stock or other ownership in Gilead Sciences. **RK:** employment with Imaging Endpoints; stock or other ownership with Teladoc, Teleview, Globavir, Verve, Renibus;

consulting or advisory role for Dynamicure, Fore Biotherapeutics, SonALAsense, Dracen, Day One, and FibroGen; patents, royalties, and other intellectual property with Imaging Endpoints. **MJK:** honoraria from and consulting/advisory role for Bristol Myers Squibb, Celgene, Kite, a Gilead Company, Miltenyi Biotech, Novartis, and Roche; research funding from Kite, Roche, Takeda, and Celgene; and travel support from Kite, Miltenyi Biotech, Novartis, and Roche.

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Tables

Table 1. Baseline MTV by treatment arm and characteristics

Treatment arm or characteristic	n/N	Median MTV (range), mL	Descriptive *P**
Treatment arm			
Axi-cel	175[†]/180	228.66 (2.3-16,669.3)	.66
Standard care	165/179	231.90 (0.04-2811.2)	
Age			
<65 years	235/250	256.57 (0.04-16,669.3)	< .01
≥65 years	105/109	176.71 (6.8-4101.8)	
Molecular subgroup, per central laboratory			
GCB	202/208	229.45 (3.5-16,669.3)	.55
Non-GCB	53/56	242.60 (6.9-5488.5)	
Disease type, per central laboratory			
HGBL	54/57	307.71 (8.5-6823.5)	.31
Non-HGBL	251/256	228.48 (0.04-16,669.3)	
LDH			
Elevated	185/195	371.17 (2.3-16,669.3)	< .01
Normal	155/164	126.96 (0.04-3712.8)	
Response to first-line therapy at randomization			
Primary refractory	252/265	236.88 (0.04-16,669.3)	.64
Relapse ≤12 months after completion of 1L therapy	87/92	215.33 (3.6-5317.7)	
CD19 positive on IHC staining			

Yes	270/278	237.92 (0.04-13,527.0)	.86
No	25/25	248.89 (3.6-16,669.3)	
CD19 H-score			
≤Median‡	149/152	241.75 (0.04-16,669.3)	.79
>Median	146/151	229.72 (2.3-13,527.0)	

*Two-sided *P* values for 2-group comparisons were calculated using Wilcoxon rank sum test.

†The initial presentation of these analyses[40] inadvertently included data from a patient who was retreated with axi-cel. Those data were removed, and only data from randomized treatment were included.

‡Median CD19 H-score was 150.

Figure Legends

Figure 1. Baseline MTV estimates from whole-body FDG PET images. Single-slice coronal FDG PET images (A and E) demonstrating hypermetabolic uptake in the original image data sets. The top row (A-D) shows hypermetabolic FDG uptake in a limited number of lesions in the abdomen and pelvis with an estimated total whole-body MTV = 231.9 mL. The middle row (E-H) shows hypermetabolic FDG uptake in soft-tissue and nodal lesions in the chest and abdomen with an estimated total whole-body MTV = 1921.7 mL. The segmented lesions containing the individual lesion masks (colored regions in B and F) are shown. Within each of these segmented lesions, masks of the FDG PET voxels with SUV values 41%-100% of SUVmax are delineated on the parametric maps (C and G). The total whole-body MTV is then calculated from the sum of delineated voxels. The arrows represent normal physiologic activity in the bladder (A and E) and GI tract (A). Images D and H are maximum intensity projection images that represent the extent of disease on the whole-body FDG PET.

Figure 2. Associations between baseline MTV and known prognostic factors. Spearman correlation estimates and *P* values from a Fisher *z* transformation were used to summarize relationships between baseline MTV and continuous baseline covariates. (A) Baseline SPD vs MTV. (B) Baseline LDH vs MTV. The fit line is based on linear regression with 95% CI limit.

Figure 3. Kaplan-Meier plots of survival outcomes by MTV and treatment arm. (A) EFS per central assessment. (B) PFS per investigator assessment. Estimated hazard ratios, 95% confidence intervals, and descriptive 2-sided *P* values were calculated from a Cox proportional-hazards model.

Figure 4. Baseline MTV by response group and treatment arm. (A) Responders vs nonresponders per central assessment. (B) Patients with ongoing response vs others per central assessment. Descriptive 2-sided *P* values for 2-group comparisons were calculated using Wilcoxon rank sum test. Extreme values are not shown.

Figure 5. Baseline MTV by grade of neurologic events and CRS in patients treated with axi-cel. (A) Neurologic events. (B) CRS. Descriptive 2-sided *P* values for 2-group comparisons were calculated using Wilcoxon rank sum test. Extreme values are not shown.

Figure 1

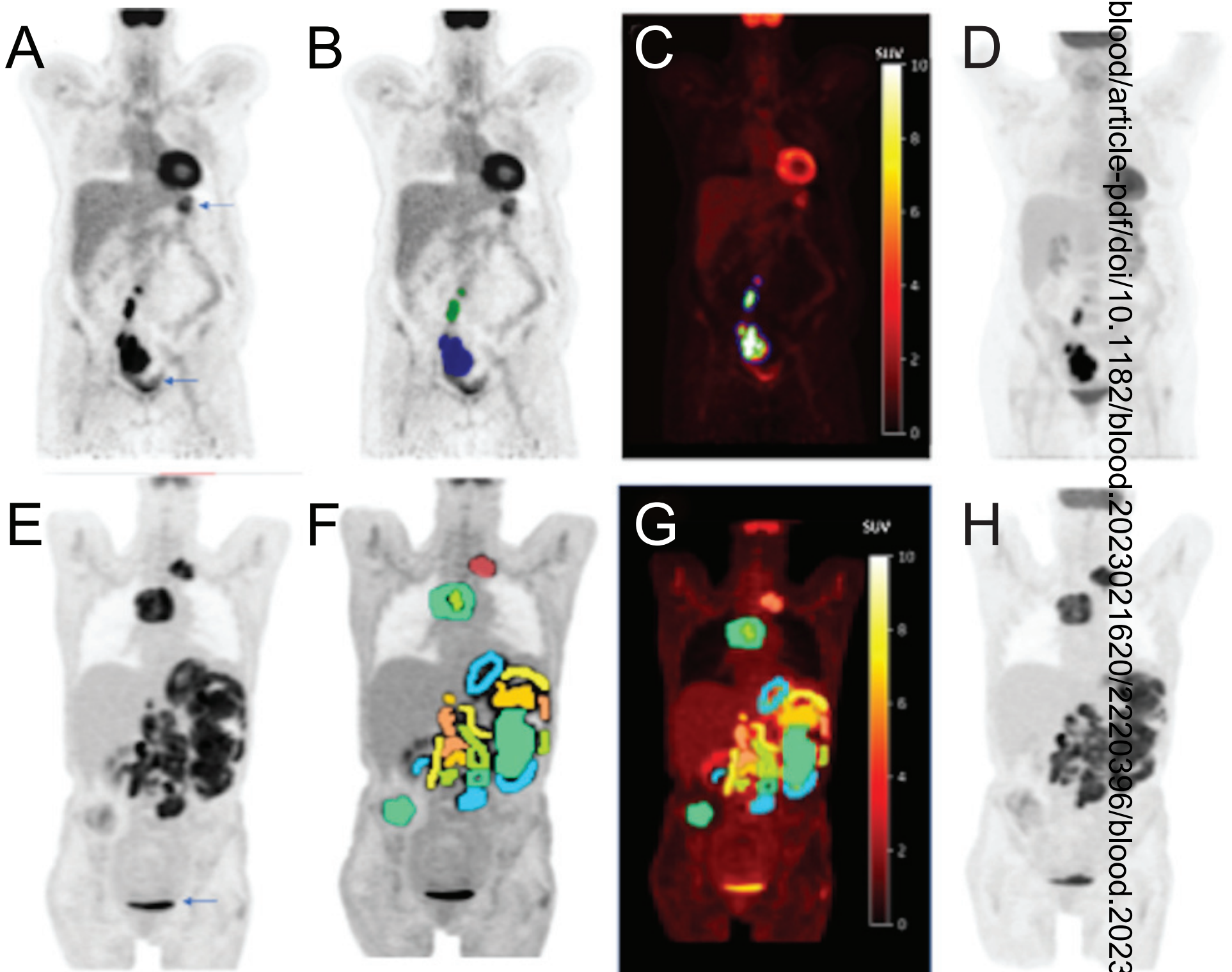
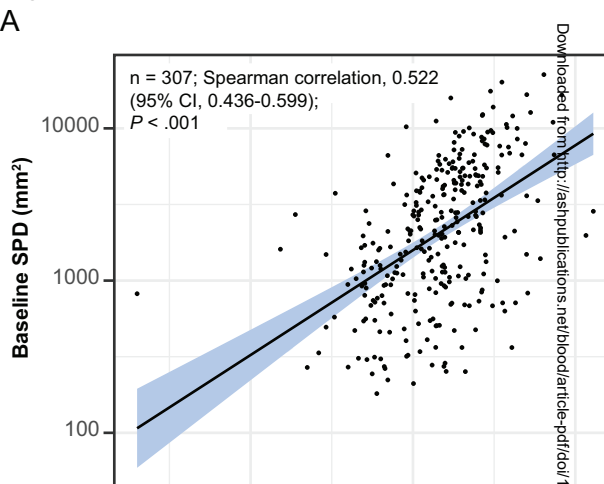


Figure 2



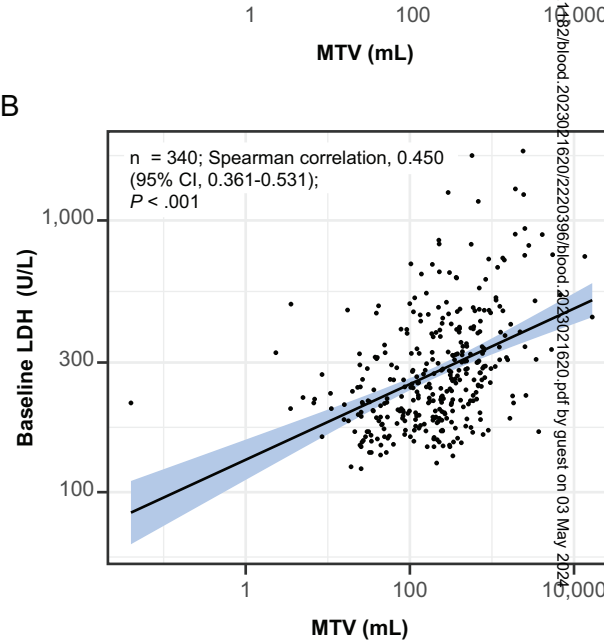
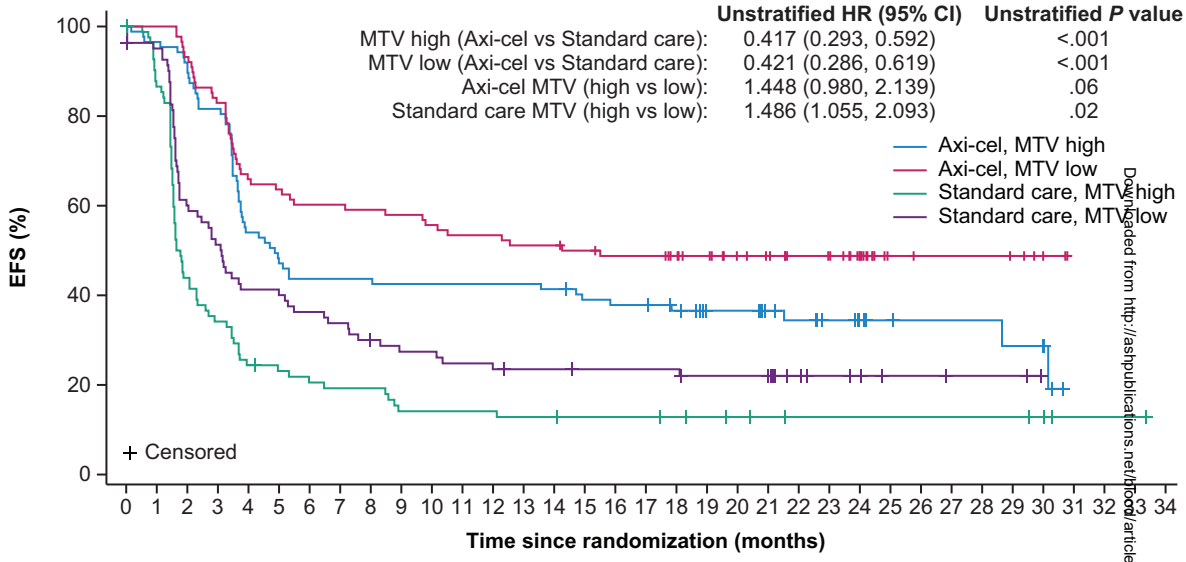


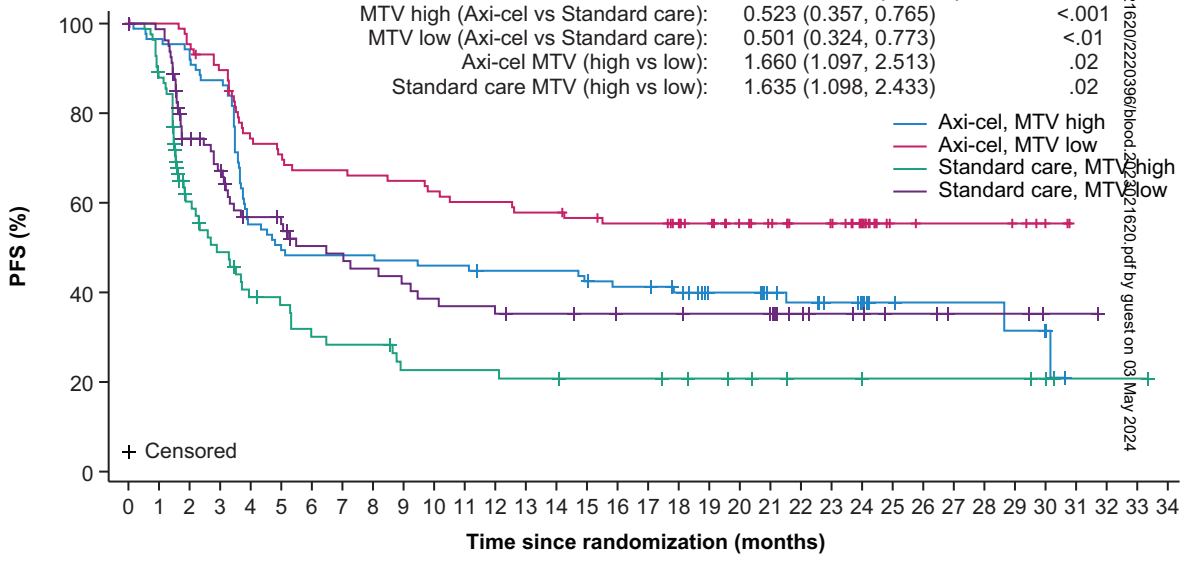
Figure 3

A



Patients at risk																															
Axi-cel, MTV high	87	84	80	71	47	41	38	38	38	37	37	37	37	37	36	33	32	32	29	22	22	18	16	13	9	7	6	6	6	5	4	0
Axi-cel, MTV low	88	88	82	73	58	56	53	53	52	51	49	47	47	45	45	43	41	41	38	35	30	28	24	23	17	7	6	6	6	5	2	0
Standard care, MTV high	83	71	36	28	20	18	16	15	15	11	11	11	11	10	10	9	9	9	8	7	6	5	4	4	4	4	4	4	4	3	1	1	1	0
Standard care, MTV low	82	76	48	41	33	32	29	27	23	21	21	19	18	17	17	16	16	16	16	14	14	13	8	6	5	3	3	2	2	2	0			

B



Patients at risk																															
Axi-cel, MTV high	87	84	82	76	48	43	42	42	42	41	40	40	38	38	38	36	34	34	31	23	23	19	17	14	10	7	6	6	6	5	4	0
Axi-cel, MTV low	88	87	83	77	63	60	57	57	56	55	53	51	51	49	49	47	45	45	42	38	33	30	26	25	18	7	6	6	6	5	2	0
Standard care, MTV high	83	72	38	30	23	21	17	16	16	12	12	12	12	11	11	10	10	10	9	8	7	6	5	5	4	4	4	4	4	4	3	1	1	1	0
Standard care, MTV low	82	79	54	47	37	35	30	29	27	25	23	22	21	20	20	19	18	18	18	17	17	16	10	8	7	5	5	3	3	3	1	1	0	

Figure 4

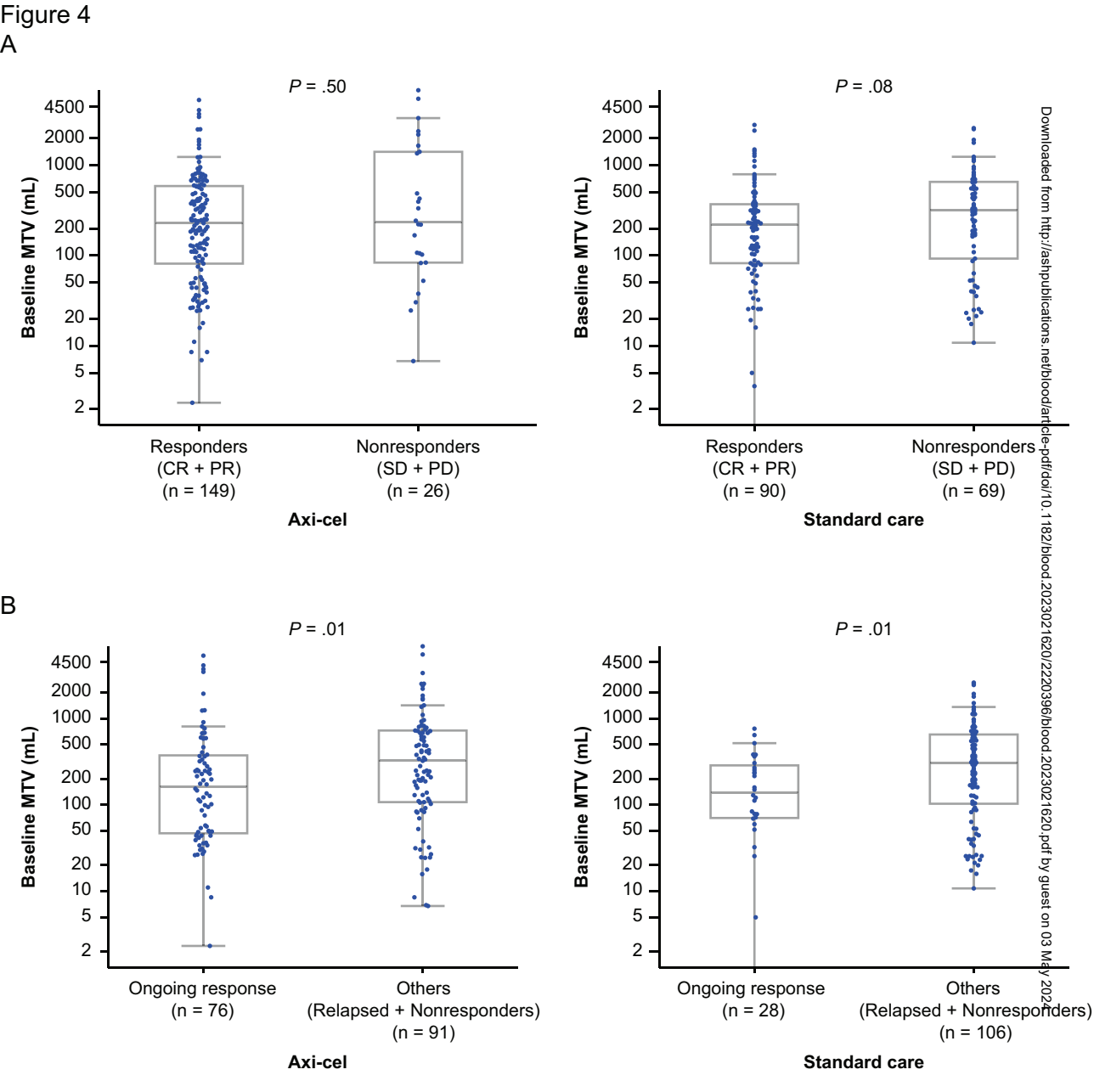
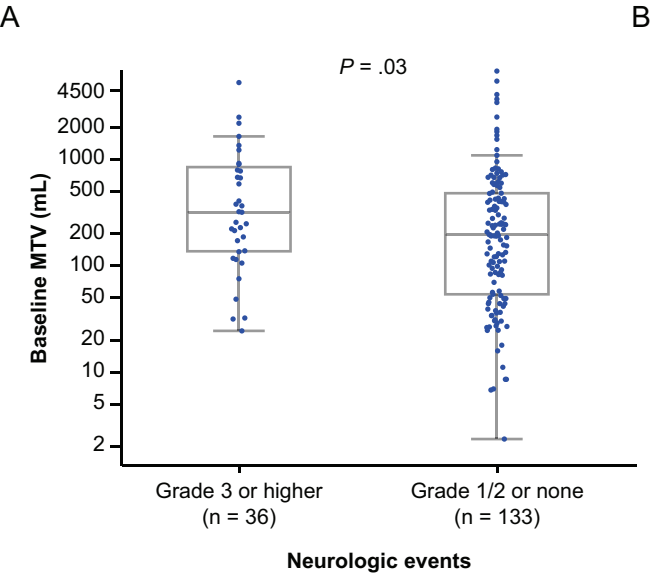
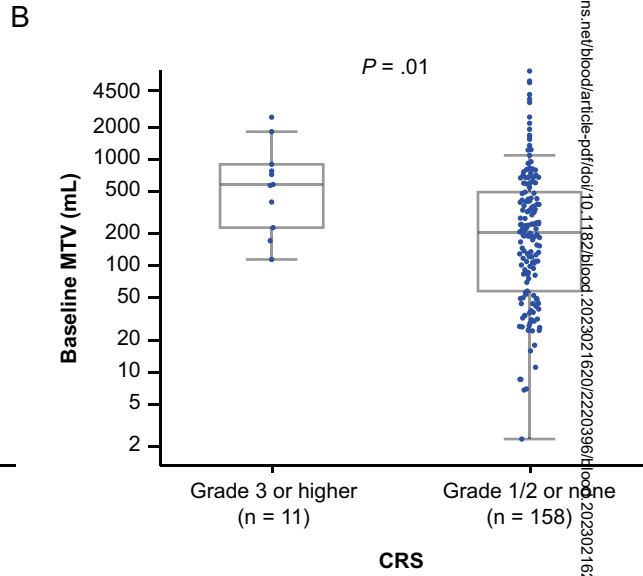


Figure 5

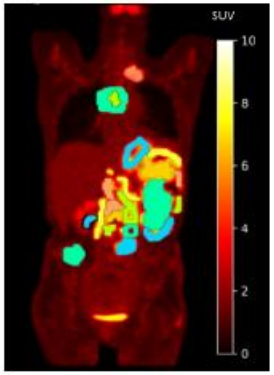




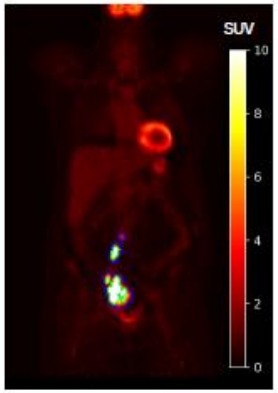
Axicabtagene Ciloleucel (Axi-Cel) Versus Standard of Care in Second-Line Large B-Cell Lymphoma: Outcomes by Metabolic Tumor Volume (MTV)

Baseline MTV ranged from 0.04 to 16,669.3 mL

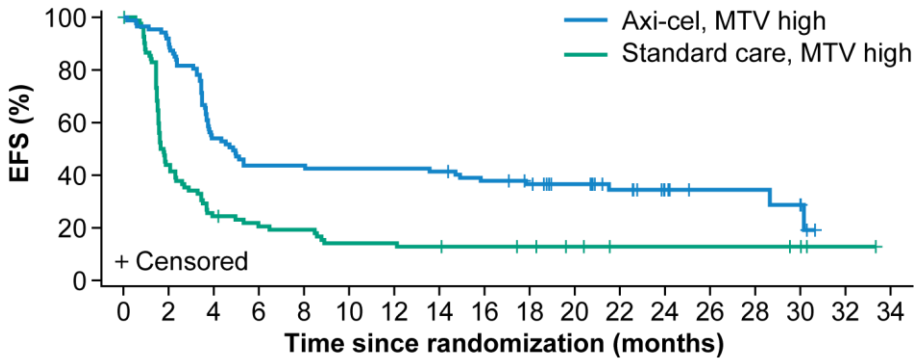
- **Example: High MTV (1921.7 mL)**

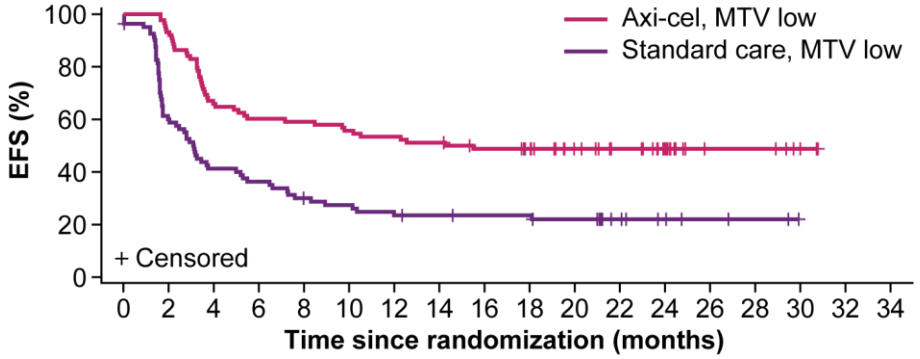


- **Example: Median MTV (231.9 mL)**



Event-free survival (EFS) in patients with high and low MTV by treatment arm





Conclusions: **Axi-Cel improved EFS over standard care for patients with high and low MTV, a whole-body measure of tumor burden.**

*Locke et al. DOI: 10.xxxx/**blood**.2024xxxxxx*

***Blood* Visual Abstract**