

SUPPLEMENTARY INFORMATION

Prognostic value of [¹⁸F]FDG PET/CT in patients with CNS lymphoma receiving ibrutinib-based therapies

Simone Krebs¹, Audrey Mauguen², Onur Yildirim³, Vaios Hatzoglou³, Jasmine H. Francis⁴, Lauren R. Schaff⁵, Ingo K. Mellinghoff⁵, Heiko Schöder^{1†*}, Christian Grommes^{5†}

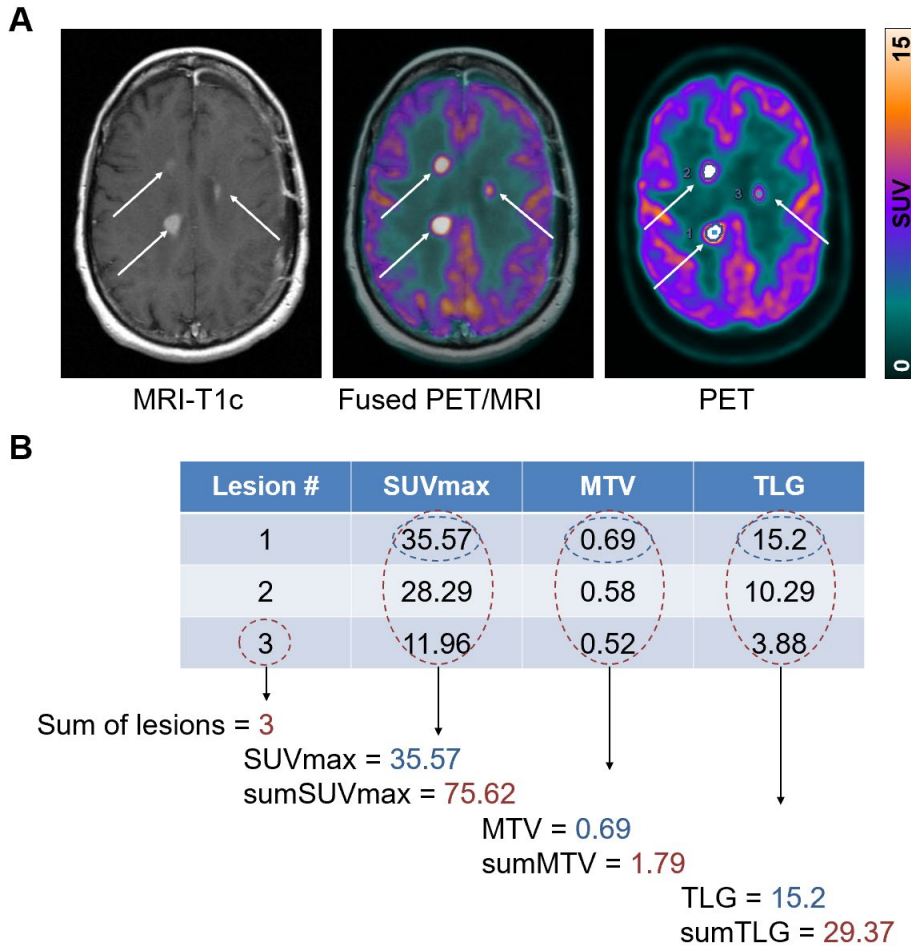
¹Molecular Imaging and Therapy Service, Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY; ²Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY; ³Neuroradiology Service, Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY; ⁴Ophthalmic Oncology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY; ⁵Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, NY

***Corresponding author:** Heiko Schöder, Molecular Imaging and Therapy Service, Memorial Sloan Kettering Cancer Center, 1275 York Ave, Box 77, New York, NY 10065; e-mail: schoderh@mskcc.org

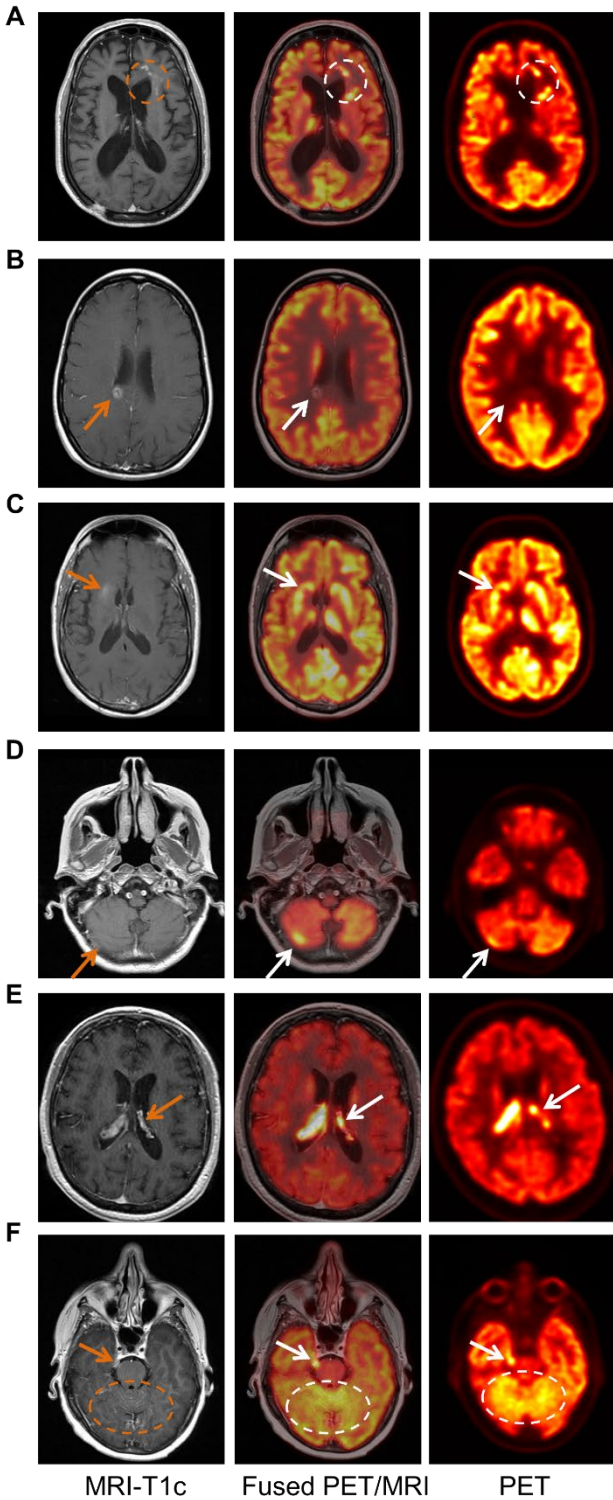
†Contributed equally as senior authors

FIGURES

Supplementary Fig. 1 Description of PET parameters in a representative patient example.

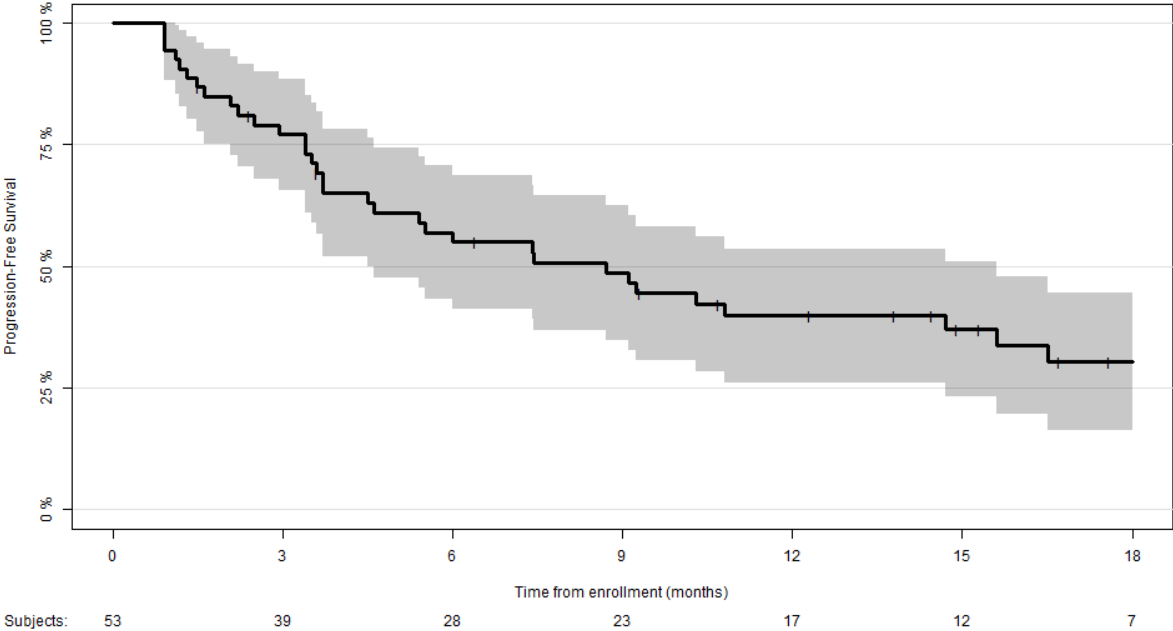


(A) Contrast-enhanced T1-weighted MRI depicts three enhancing lesions; axial fused PET/MRI and PET images confirming focal [¹⁸F]FDG uptake. (B) Display and calculation of PET parameters.

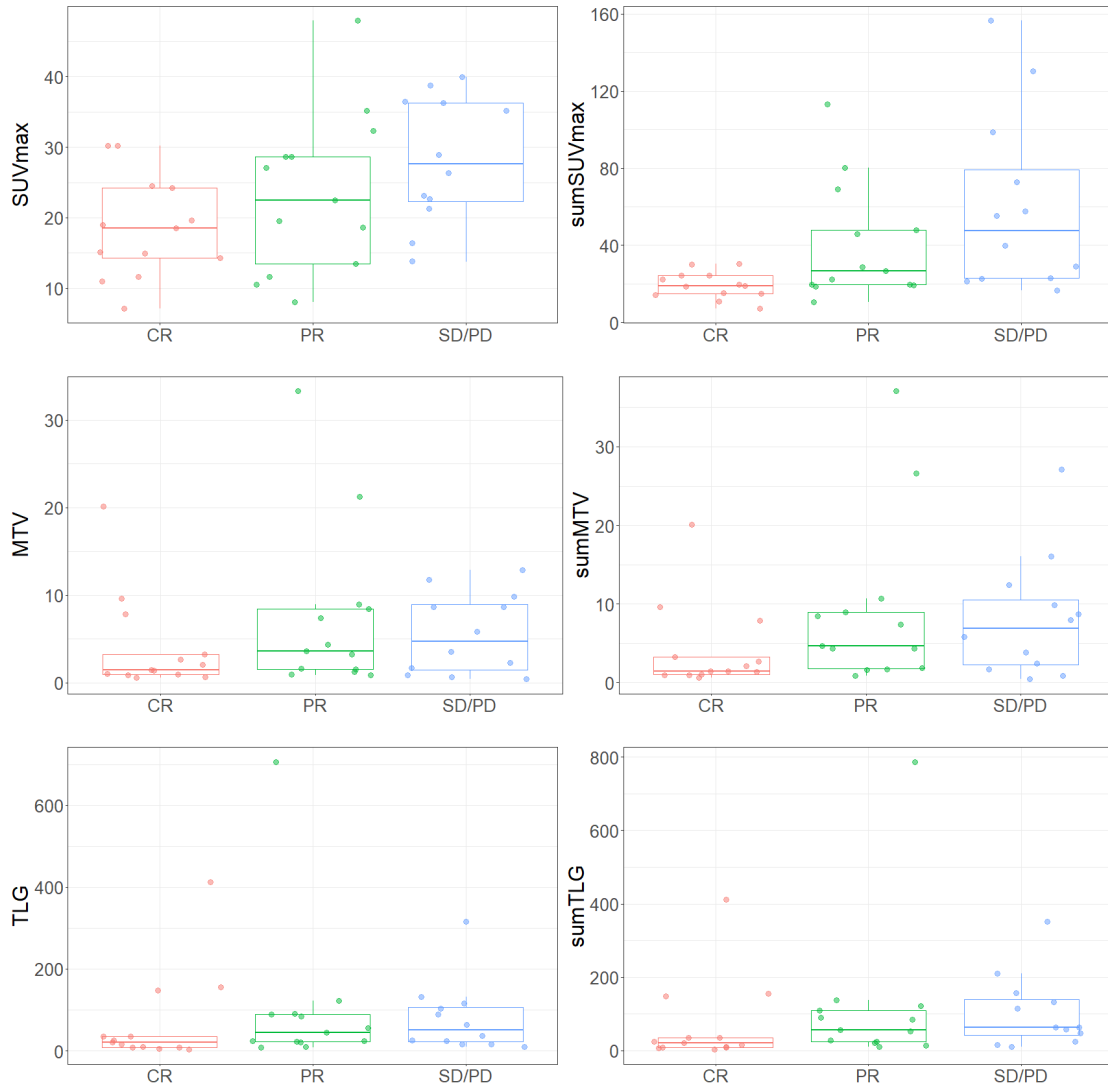


Supplementary Fig. 2 Spectrum of imaging patterns in CNS lymphoma. Contrast-enhanced (CE) T1-weighted MRI (left), fused PET/MRI (mid), and PET images (right). (A) Heterogeneous lesion. (B) Nodular enhancing lesion in right posterior body of corpus callosum. (C) Ill-defined enhancement in right anterior basal ganglia, possibly obscured on PET by physiologic intense uptake. (D) Focal avidity in right cerebellar hemisphere without enhancement on MRI and without correlate on FLAIR images (not shown). (E) Lesion in choroid plexus in left ventricle better seen on PET than on MRI, possibly obscured by physiologic intense enhancement in choroid plexus. (F) Diffuse enhancement and thickening of bilateral cranial nerves V, most conspicuous on the right (arrow), showing uptake on PET. Leptomeningeal enhancement involving cerebellar folia (circle) shows elevated metabolic activity.

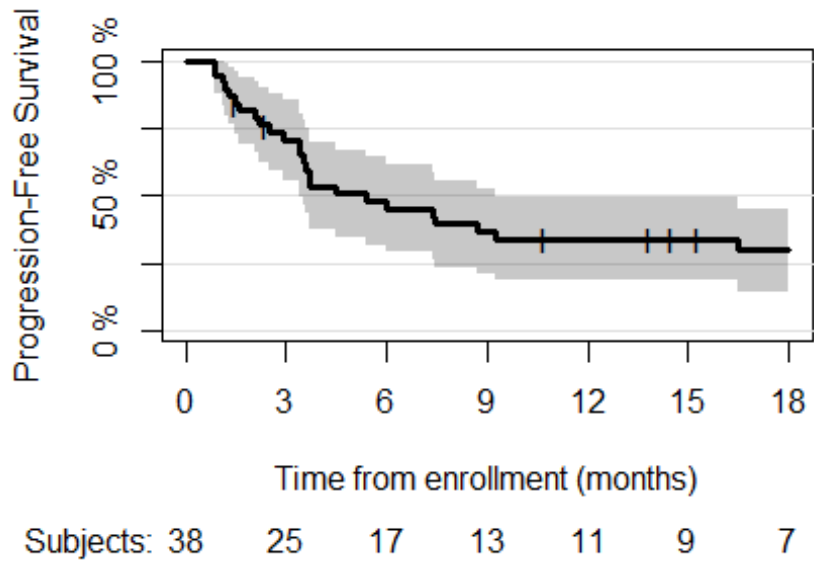
Supplementary Fig. 3 Progression-free survival curve (Kaplan-Meier estimate) for the 53 patients.



Supplementary Fig. 4 Distribution of PET parameters by overall response rate (ORR) for the 38 patients with clearly PET-positive lesions. Center lines show the medians; box limits indicate the 25th and 75th percentiles; whiskers extend 1.5 times the interquartile range from the 25th and 75th percentiles. n =13 CR, 13 PR, 12 SD/PD.



Supplementary Fig. 5 Progression-free survival curve (Kaplan-Meier estimate) for the 38 patients with clearly PET-positive lesions.



TABLES

Supplementary Table 1 Correlation between PET parameters and tumor volume for the 53 patients.

Parameters	Spearman	95% CI Spearman	Pearson	95% CI Pearson
sumSUV _{max}	0.631	CI: 0.413 - 0.780	0.599	CI: 0.392 - 0.748
SUV _{max}	0.640	CI: 0.425 - 0.787	0.622	CI: 0.423 - 0.764
sumMTV	0.682	CI: 0.482 - 0.815	0.594	CI: 0.386 - 0.745
MTV	0.668	CI: 0.463 - 0.805	0.586	CI: 0.375 - 0.739
sumTLG	0.714	CI: 0.526 - 0.835	0.619	CI: 0.419 - 0.762
TLG	0.704	CI: 0.512 - 0.829	0.616	CI: 0.415 - 0.760

CI = Confidence Interval.

Supplementary Table 2 Distribution of PET parameters and MYD88 mutation status for the 53 patients.

Characteristic	Mutated, N = 28¹	Wild Type, N = 22¹	p-value²
sumSUV _{max}	19 (3, 130)	20 (3, 157)	0.89
SUV _{max}	16 (3, 40)	17 (3, 48)	0.87
sumMTV	2 (0, 37)	1 (0, 27)	0.51
MTV	1.9 (0.0, 33.3)	1.0 (0.0, 11.7)	0.44
sumTLG	25 (0, 787)	20 (0, 209)	0.50
TLG	23 (0, 707)	15 (0, 148)	0.41

¹Statistics presented: median (minimum, maximum)

²Statistical tests performed: Wilcoxon rank-sum test

Supplementary Table 3 Distribution of PET parameters and CD79B status for the 53 patients.

Characteristic	Mutated, N = 21¹	Wild Type, N = 30¹	p-value²
sumSUV _{max}	19 (3, 130)	20 (3, 157)	0.42
SUV _{max}	16 (3, 40)	17 (3, 48)	0.61
sumMTV	2 (0, 20)	3 (0, 37)	0.24
MTV	0.9 (0.0, 20.1)	1.6 (0.0, 33.3)	0.22
sumTLG	16 (0, 412)	30 (0, 787)	0.43
TLG	16 (0, 412)	24 (0, 707)	0.39

¹Statistics presented: median (minimum, maximum)

²Statistical tests performed: Wilcoxon rank-sum test

Supplementary Table 4 Summary of PET parameters by ORR for the 53 patients.

Characteristic	CR, N = 24¹	PR, N = 16¹	SD/PD, N = 13¹
sumSUV _{max}	9, (3, 19), (3-30)	21, (17, 46), (3-113)	40, (23, 73), (3-157)
SUV _{max}	9, (3, 19), (3-30)	19, (10, 29), (3-48)	26, (21, 36), (3-40)
sumMTV	1, (0, 2), (0-20)	4, (1, 9), (0-37)	6, (2, 10), (0-27)
MTV	0.6, (0.0, 1.6), (0.0-20.1)	2.4, (0.9, 7.6), (0.0-33.3)	3.6, (0.9, 8.7), (0.0-12.8)
sumTLG	5, (0, 22), (0-412)	40, (14, 95), (0-787)	63, (25, 132), (0-352)
TLG	4, (0, 22), (0-412)	24, (9, 85), (0-707)	37, (16, 102), (0-315)

¹Statistics presented: median, (IQR), (minimum-maximum)

SD and PD were grouped as non-responders due to their small frequencies.

Supplementary Table 5 Correlation between PET parameters and tumor volume for the 38 patients with clearly PET-positive lesions.

Parameters	Spearman	95%CI Spearman	Pearson	95%CI Pearson
sum SUVmax	0.394	CI: 0.072 - 0.641	0.415	CI: 0.11 - 0.649
max SUVmax	0.395	CI: 0.074 - 0.642	0.505	CI: 0.221 - 0.71
sum MTV	0.558	CI: 0.267 - 0.756	0.402	CI: 0.094 - 0.639
max MTV	0.532	CI: 0.235 - 0.738	0.381	CI: 0.07 - 0.625
sum TLG	0.612	CI: 0.337 - 0.791	0.526	CI: 0.248 - 0.724
max TLG	0.597	CI: 0.318 - 0.781	0.507	CI: 0.224 - 0.711

Supplementary Table 6 Distribution of PET parameters and MYD88 mutation status for the 38 patients with clearly PET-positive lesions.

Characteristic	MUT, N = 21¹	WT, N = 15¹	p-value²
sum SUVmax	23 (7, 130)	24 (11, 157)	0.37
max SUVmax	20 (7, 40)	23 (11, 48)	0.70
sum MTV	6 (0, 37)	4 (1, 27)	0.70
max MTV	3.6 (0.4, 33.3)	2.3 (0.7, 11.7)	0.57
sum TLG	56 (2, 787)	53 (8, 209)	0.68
max TLG	45 (2, 707)	24 (5, 148)	0.51

¹Statistics presented: median (minimum, maximum)

²Statistical tests performed: Wilcoxon rank-sum test

Supplementary Table 7 Distribution of PET parameters and CD79B status for the 38 patients with clearly PET-positive lesions.

Characteristic	MUT, N = 14¹	WT, N = 23¹	p-value²
sum SUVmax	25 (7, 130)	23 (11, 157)	0.75
max SUVmax	21 (7, 40)	23 (8, 48)	0.90
sum MTV	3 (0, 20)	4 (1, 37)	0.36
max MTV	2.7 (0.4, 20.1)	3.3 (0.7, 33.3)	0.31
sum TLG	31 (2, 412)	56 (7, 787)	0.77
max TLG	30 (2, 412)	35 (5, 707)	0.70

¹Statistics presented: median (minimum, maximum)

²Statistical tests performed: Wilcoxon rank-sum test

Supplementary Table 8 Summary of PET parameters by ORR for the 38 patients with clearly PET-positive lesions.

Characteristic	CR, N = 13¹	PR, N = 13¹	SD/PD, N = 12¹
sum SUVmax	19, (15, 24), (7-30)	27, (20, 48), (11-113)	48, (23, 79), (16-157)
max SUVmax	19, (14, 24), (7-30)	22, (13, 29), (8-48)	28, (22, 36), (14-40)
sum MTV	1, (1, 3), (1-20)	5, (2, 9), (1-37)	7, (2, 11), (0-27)
max MTV	1.4, (1.0, 3.3), (0.6-20.1)	3.6, (1.6, 8.4), (0.9-33.3)	4.7, (1.5, 9.0), (0.4-12.8)
sum TLG	21, (9, 35), (2-412)	56, (24, 110), (10-787)	63, (42, 139), (10-352)
max TLG	21, (8, 35), (2-412)	45, (22, 90), (8-707)	50, (22, 106), (10-315)

¹Statistics presented: median, (IQR), (minimum-maximum)

SD and PD were grouped as non-responders due to their small frequencies.

Supplementary Table 9 Univariable PFS analysis for the PET parameters for the 38 patients with clearly PET-positive lesions.

Characteristic	HR¹	95% CI¹	p-value
max SUVmax	1.04	1.00, 1.09	0.04
sum SUVmax	1.02	1.01, 1.03	0.005
log-max MTV	1.10	0.77, 1.57	0.60
log-sum MTV	1.22	0.86, 1.73	0.26
log-max TLG	1.09	0.83, 1.45	0.54
log-sum TLG	1.18	0.89, 1.56	0.25

¹HR = Hazard Ratio, CI = Confidence Interval

Supplementary Table 10 Univariable PFS analysis for the clinical parameters for the 38 patients with clearly PET-positive lesions.

Characteristic	N	HR¹	95% CI¹	p-value
Age	38	0.98	0.94, 1.01	0.20
ECOG	38			0.84
0		Ref.		
1		1.30	0.47, 3.60	
2		1.06	0.28, 3.96	
Treatment	38			0.02
Combination		Ref.		
Single agent		2.95	1.09, 7.98	
MYD88	36			0.82
MUT		Ref.		
WT		0.91	0.40, 2.08	
CD79B	37			0.85
MUT		Ref.		
WT		1.08	0.47, 2.48	
N lesions	38			0.11
1		Ref.		
2+		1.95	0.88, 4.35	
log-Total tumor volume (cm³)	38	1.15	0.94, 1.40	0.15

¹HR = Hazard Ratio, CI = Confidence Interval

Supplementary Table 11 Multivariable analysis for PFS for the 38 patients with clearly PET-positive lesions.

Characteristic	HR¹	95% CI¹	p-value
sum SUVmax (for 5 units)	1.11	1.01, 1.22	0.03
log-sum MTV	1.46	0.44, 4.77	0.54
log-sum TLG	0.65	0.25, 1.70	0.38
Treatment			0.11
Combination	Ref.		
Single agent	2.43	0.77, 7.67	
N lesions			0.56
1	Ref.		
2+	0.66	0.16, 2.76	
log-Total tumor volume (cm ³)	1.04	0.79, 1.37	0.78

¹HR = Hazard Ratio, CI = Confidence Interval

Supplementary Table 12 Multivariable analysis for PFS (reduced Cox model after variable selection) for the 38 patients with clearly PET-positive lesions.

Characteristic	HR¹	95% CI¹	p-value
sum SUVmax (for 5 units)	1.09	1.03, 1.16	0.005

¹HR = Hazard Ratio, CI = Confidence Interval