Supplemental Tables and Figures - MS#ADV-2021-006923R3

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Supplemental Figure 4. Kaplan-Meier estimates of survival (progression-free and overall) according to risk groups based on the risk factors TMTV >220 cm^3 and ECOG-PS ≥2 in the PETAL (A, B), GOYA (C,D) and real-world (E,F) series in patients aged ≥60 years.

Supplemental Table 1. Main characteristics of the two clinical trials (GOYA, PETAL) and the real-world series

Study name	Clinical trial identifier Phase N patients	Inclusion period	N centers and location	Patient characteristics	Treatment
GOYA	NCT01287741 Phase III n=1315	July 2011 to June 2014	207 centers in 29 countries	Previously untreated DLBCL, ECOG-PS 0-2, and either IPI ≥2 or IPI = 1 with or without bulky disease (defined as one lesion ≥ 7.5 cm), or with an IPI = 0 and bulky disease, aged ≥ 18 years	Obinutuzumab (Gazyva/Gazyvaro) G-CHOP versus R-CHOP
PETAL	NCT00554164 Phase III n= 510	November 2007 to December 2012	23 German centers	Untreated aggressive CD20-positive lymphoma with ECOG-PS 0-3 (patients with T-cell lymphoma were excluded)	After 2 cycles of R-CHOP, PET-positive patients with untreated aggressive CD20-positive lymphoma with ECOG-PS ≤3 were randomly assigned to treatment, 4 cycles of R-CHOP ±2 additional doses of rituximab
Real world series	n=349	2004 to 2016	4 European centers	Patients aged ≥ 18 years, with DLBCL	R-CHOP, 6 or 8 cycles

Supplemental Table 2. Clinical characteristics of patients stratified by age (<60 years and ≥60 years) and by series

Characteristic, n (%)	Age <60 years			Age ≥60 years		
	PETAL (n = 229)	GOYA (n = 557)	Real-world series (n = 94)	PETAL (n=280)	GOYA (n=758)	Real-world series (n=234)
Median age, years (range)	50 (18-59)	49 (18-59)	48.5 (17-59)	69 (60-80)	68 (60-86)	69 (60-80)
Sex						
Male	126 (55.0)	245 (44.0)	53 (56.4)	153 (54.6)	386 (50.9)	109 (46.6)
Female	103 (45.0)	312 (56.0)	41 (43.6)	127 (45.4)	372 (49.1)	125 (53.4)
Histology						
DLBCL NOS	198 (86.5)	508 (91.2)	16 (84.2)	280 (100)	678 (89.4)	155 (92.3)
FL grade 3B	14 (6.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
De novo transformed	17 (7.4)	0 (0)	0 (0)	0 (0)	0 (0)	10 (6.0)
Other	0 (0)	49 (8.8)	3 (15.8)	0 (0)	80 (10.6)	3 (1.8)
Missing	0	0	75	0	0	66
ECOG-PS						
0–1	211 (93.4)	490 (88.0)	79 (84.0)	240 (86.0)	662 (87.3)	167 (71.4)
≥ 2	15 (6.6)	67 (12.0)	15 (16.0)	39 (14.0)	96 (12.7)	67 (28.6)
Missing	3	0	0	0	0	0
Ann Arbor stage						
I-II	101 (44.3)	135 (24.2)	39 (41.5)	113 (40.4)	179 (23.6)	49 (20.9)
III-IV	127 (55.7)	422 (75.8)	55 (58.5)	167 (59.6)	579 (76.4)	185 (79.1)
Missing	1	0	0	0	0	0
Extranodal sites						
< 2	156 (68.4)	353 (63.4)	61 (64.9)	193 (68.9)	501 (66.1)	138 (62.2)
≥ 2	72 (31.6)	204 (36.6)	33 (35.1)	87 (31.1)	257 (33.9)	84 (37.8)
Missing	0	0	1	0	0	12
Elevated LDH (> ULN)						

Characteristic, n (%)	Age <60 years			Age ≥60 years		
	PETAL (n = 229)	GOYA (n = 557)	Real-world series (n = 94)	PETAL (n=280)	GOYA (n=758)	Real-world series (n=234)
No	101 (44.3)	235 (42.2)	40 (43.0)	121 (43.2)	323 (42.6)	82 (35.0)
Yes	127 (55.7)	322 (57.8)	53 (57.0)	159 (56.8)	431 (56.9)	152 (65.0)
Missing	1	0	1	0	4	0
aaIPI						
0–1	137 (60.4)	293 (52.6)	50 (53.2)	153 (54.6)	393 (51.8)	89 (38.0)
2–3	90 (39.7)	264 (47.4)	44 (46.8)	127 (45.4)	365 (48.2)	145 (62.0)
IPI						
0-2	176 (77.2)	417 (74.9)	60 (63.8)	138 (49.3)	319 (42.1)	76 (32.5)
3-5	52 (22.8)	140 (25.1)	34 (36.2)	142 (50.7)	439 (57.9)	158 (67.5)
Missing	1	0	0	0	0	0
Treatment						
R-CHOP	222 (96.9)	274 (49.2)	94 (100)	263 (93.9)	380 (50.1)	234 (100)
G-CHOP	-	283 (50.8)	-	-	378 (49.9)	-
Intensified CHOP / CHOP	7 (3.1)	-	-	17 (6.1)	-	-
TMTV						
Median cm^3 (range)	178 (1-6750)	311.7 (2-8113)	153 (0-2416)	173 (1-8896)	250.8 (1.7-5334)	207.2 (0-3764)
TMTV >220 cm^3	109 (47.6)	333 (59.8)	34 (36.2)	121 (43.2)	392 (51.7)	114 (48.7)
TMTV and ECOG-PS risk factors						
0 factor	119 (52.0)	207 (37.2)	56 (59.6)	151 (54.1)	346 (45.6)	98 (41.9)
1 factor	96 (41.9)	300 (53.9)	27 (28.7)	96 (34.4)	336 (44.3)	91 (38.9)
2 factors	14 (6.1)	50 (9.0)	11 (11.7)	32 (11.5)	76 (10.0)	45 (19.2)

* TMTV > 220 cm^3 and ECOG-PS ≥2

Supplemental Table 3 .Calibration methodology

Initially proposed for microarrays and then validated for several imaging biomarkers in PET (Orlhac et al J Nucl Med 2018), CT (Orlhac et al Radiology 2019) and MR (Orlhac et al Eur Rad 2021), the ComBat approach estimates the location (mean) and/or scale (variance) (L/S) adjustments needed to align the statistical distributions of a given biomarker measured under different conditions. Here, we applied this approach to all patients from the phase III GOYA trial (NCT01287741) with available TMTV to a cohort within the phase III REMARC trial (NCT01122472).

Following the language as described for microarrays in ComBat, assuming $TMTV_{ij}$ represents the total metabolic tumor volume for sample *j* from clinical trial *i*. We define a L/S model that assumes:

$$\mathrm{TMTV}_{ij} = \alpha + X\beta + \gamma_i + \delta_i e_{ij}$$

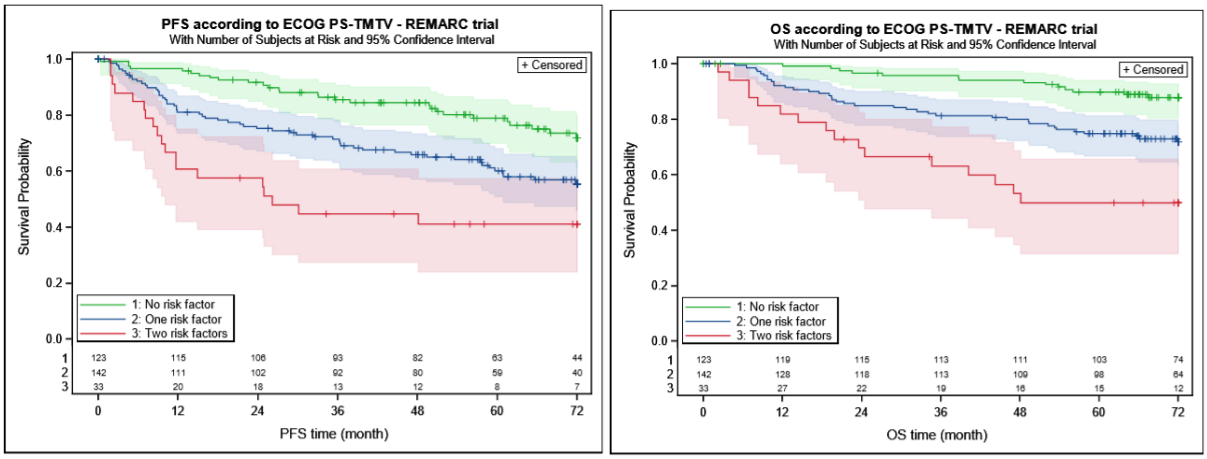
where is the overall TMTV expression, X is a design matrix for sample conditions, and is the vector of regression coefficients corresponding to X. The error terms, ijcan be assumed to follow a Normal distribution with expected value of zero and variance 2.The I and j represent the additive and multiplicative trial effects for trial *i*. The trial-adjusted data, $TMTV_{ij}$, are given by

$$\mathrm{TMTV}^{*}_{ij} = \frac{\mathrm{TMTV}_{ij} - \hat{\alpha} + X\hat{\beta} - \hat{\gamma_i}}{\hat{\delta_i}} + \hat{\alpha} + X\hat{\beta}$$

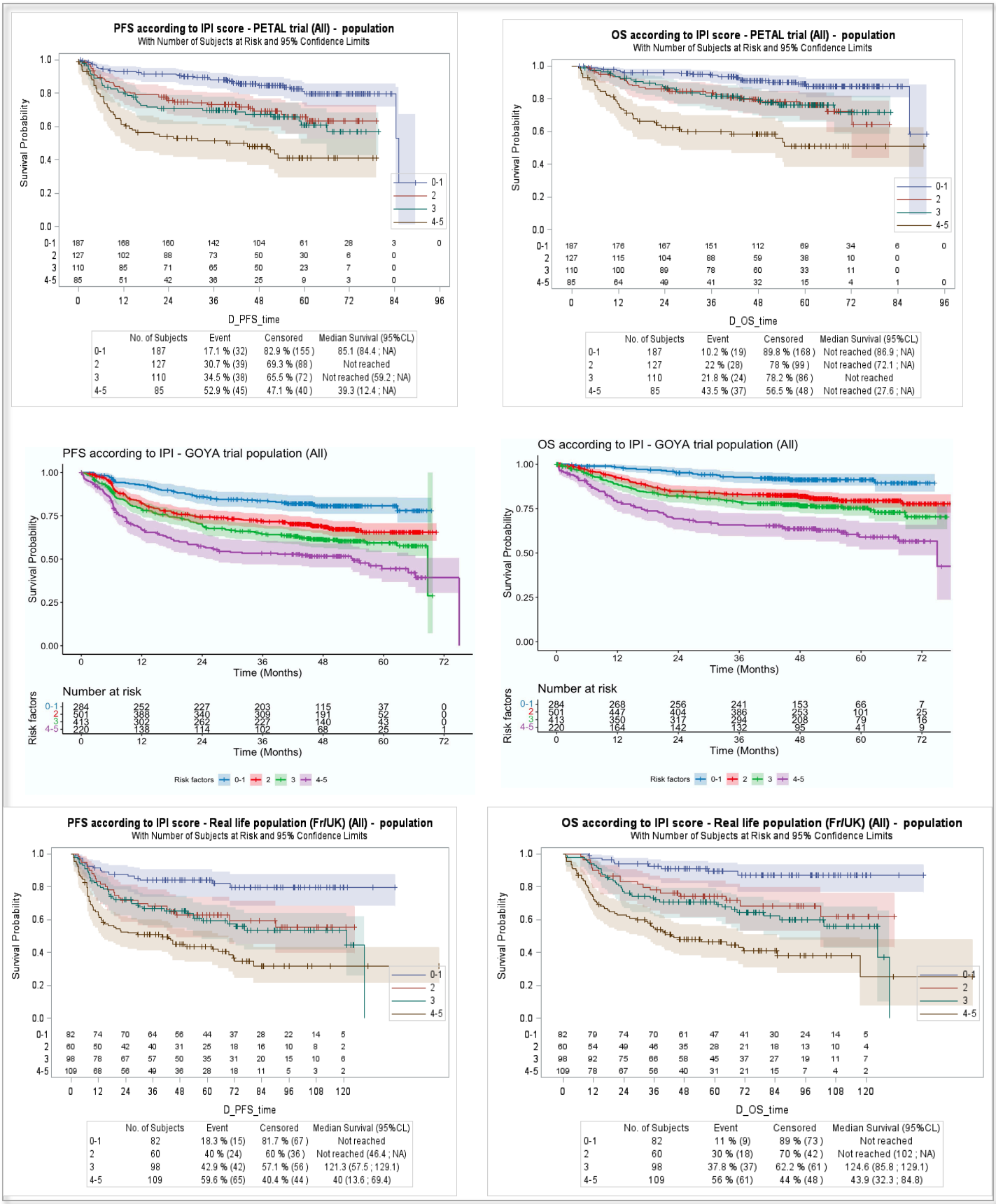
Where $\hat{\alpha}, \hat{\beta}, \hat{\gamma_i}, \text{and } \hat{\delta}_i$ are the estimators for respective parameters $\alpha, \beta, \gamma_i, \text{and } \delta_i$.

We applied the ComBat L/S adjustment to 1315 patients with available TMTV measurements from the phase III GOYA trial and leveraged 301 patients from the phase III REMARC trial as a reference using study and age ≥60 years as an indicator variable in our model matrix.

Supplemental Figure 1. Kaplan-Meier estimates of survival (progression-free and overall) according to risk groups based on the risk factors TMTV >220 cm^3 and ECOG-PS ≥2, in the REMARC study.

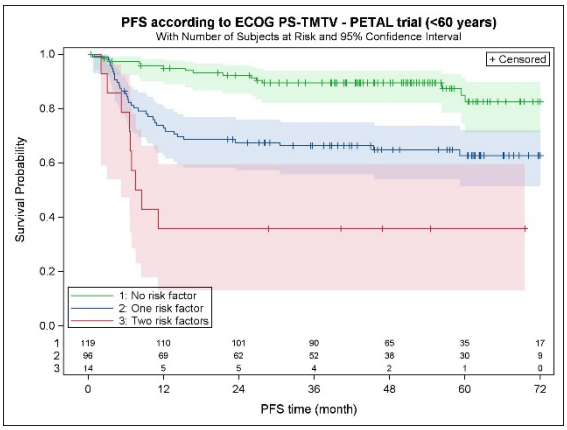


Supplemental Figure 2. Kaplan-Meier estimates of survival (progression-free and overall) according to risk groups based on the IPI.



Supplemental Figure 3. Kaplan-Meier estimates of survival (progression-free and overall) according to risk groups based on the risk factors TMTV >220 cm^3 and ECOG-PS ≥2 in the PETAL (A, B), GOYA (C,D) and real-world (E,F) series in patients aged <60 years.

A



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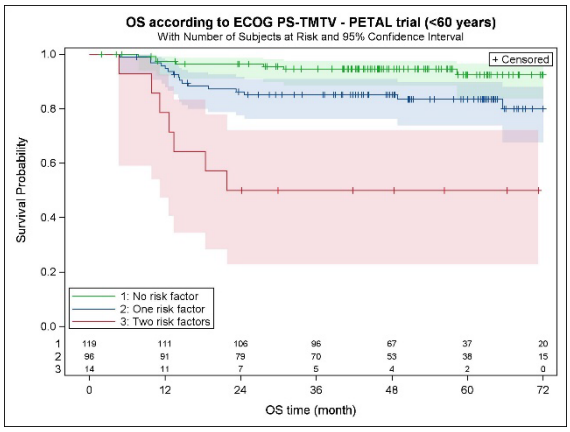

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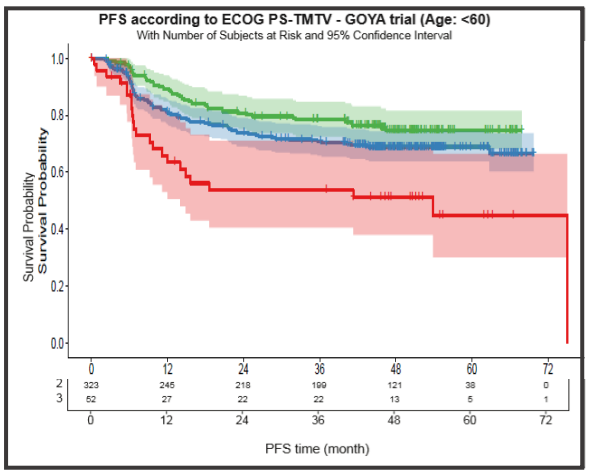

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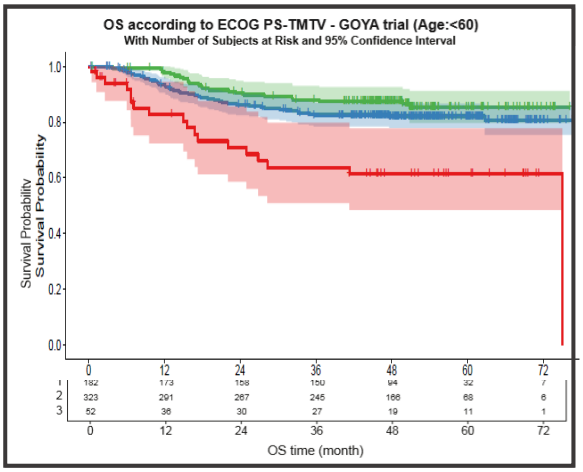

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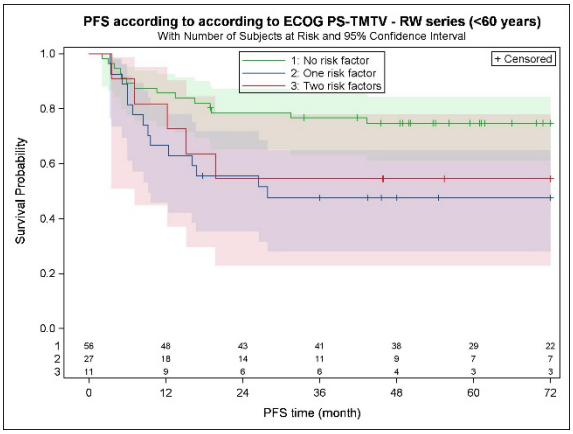

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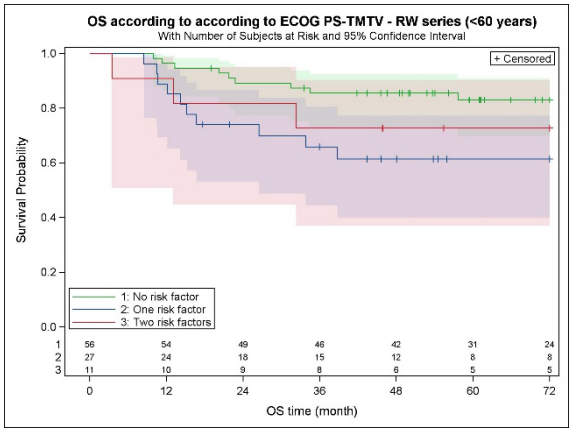
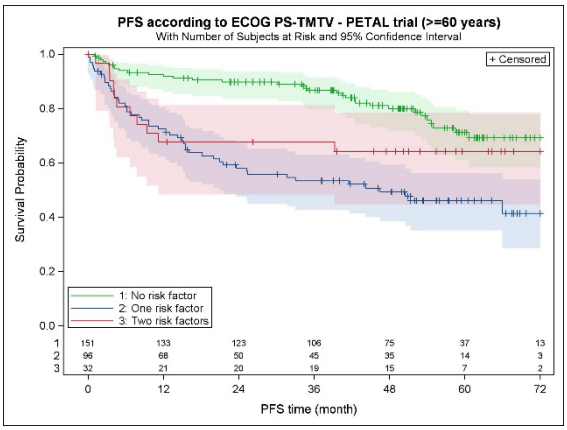


Supplemental Figure 4. Kaplan-Meier estimates of survival (progression-free and overall) according to risk groups based on the risk factors TMTV >220 cm^3 and ECOG-PS ≥2 in the PETAL (A, B), GOYA (C,D) and real-world (E,F) series in patients aged ≥60 years.

A



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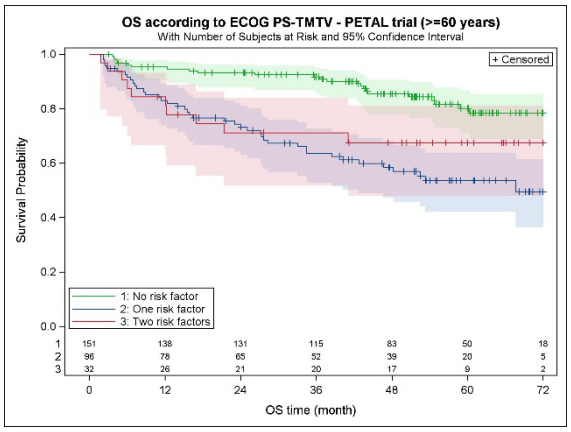

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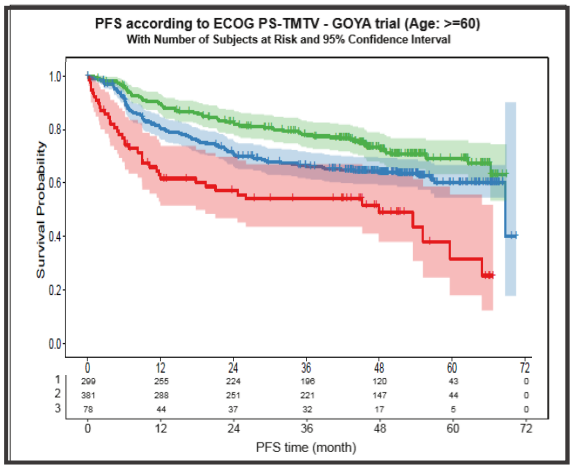

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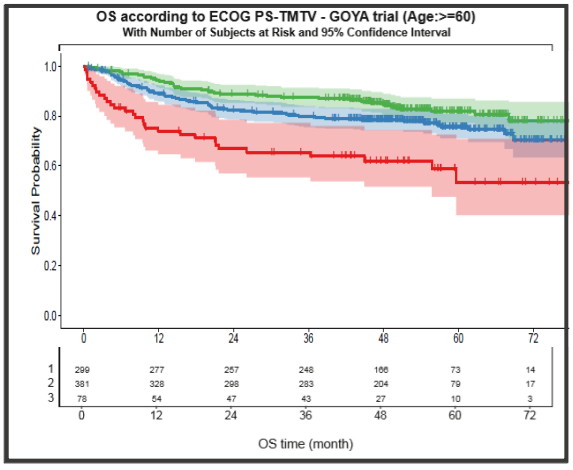

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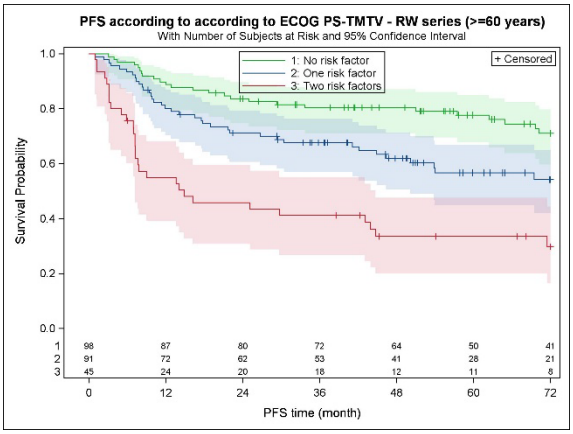

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