

*Article*

**The Pan-Immune-Inflammation Value is a new prognostic biomarker in metastatic colorectal cancer: results from a pooled-analysis of the *Valentino* and TRIBE first-line trials**  
Running title: *Pan-Immune-Inflammation Value in colorectal cancer*

## **SUPPLEMENTARY INFORMATION**

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**Supplementary Table S1. Patients' characteristics in the pooled population and in the separate subgroups of patients included from the *Valentino* study and the TRIBE study.**

Characteristics	Pooled population (N=438) N (%)	<i>Valentino</i> study (N=207) N (%)	TRIBE study (N=231) N (%)
<b>Age (years)</b>			
Median	62	62	60
IQR	53-68	54-69	53-67
<b>Gender</b>			
Female	163 (37)	67 (32)	96 (42)
Male	275 (63)	140 (68)	135 (58)
<b>ECOG PS</b>			
0	356 (81)	153 (74)	203 (88)
1	82 (19)	54 (26)	28 (12)
<b>Prior adjuvant treatment</b>			
No	376 (86)	176 (85)	200 (87)
Yes	62 (14)	31 (15)	31 (13)
<b>Primary tumour resected</b>			
No	133 (30)	55 (27)	56 (24)
Yes	305 (70)	130 (63)	175 (76)
<b>Liver-limited disease</b>			
No	307 (70)	132 (64)	175 (76)
Yes	131 (30)	75 (36)	56 (24)
<b>Synchronous metastases</b>			
No	97 (22)	44 (21)	53 (23)
Yes	341 (78)	163 (79)	178 (77)
<b>Number of metastatic sites</b>			
1	181 (41)	117 (57)	64 (28)
> 1	257 (59)	90 (43)	167 (72)
<b>Primary tumour sidedness</b>			
Left	330 (75)	178 (86)	152 (66)
Right	108 (25)	29 (14)	79 (34)
<b>RAS/BRAF status</b>			
RAS/BRAF wild-type	276 (63)	207 (100)	69 (30)
RAS mutated	146 (33)	0 (0)	146 (63)
BRAF mutated	16 (4)	0 (0)	16 (7)
<i>Abbreviations.</i> ECOG: Eastern Cooperative Oncology Group; PS: performance status.			

**Supplementary Table S2. Pan-immune-Inflammation Value (PIV) according to patients' and disease baseline characteristics.**

<b>Characteristics</b>	<b>PIV Median (IQR)</b>	<b><i>p</i>*</b>
<b>Gender</b>		0.666
Female (N=163)	396 (230-800)	
Male (N=275)	418 (250-754)	
<b>ECOG PS</b>		<b>&lt;0.001</b>
0 (N=356)	368 (228-700)	
1 (N=82)	568 (377-1578)	
<b>Prior adjuvant treatment</b>		<b>0.032</b>
No (N=376)	426 (261-794)	
Yes (N=62)	340 (181-606)	
<b>Primary tumour resected</b>		<b>&lt;0.001</b>
No (N=133)	557 (292-1005)	
Yes (N=305)	364 (221-679)	
<b>Liver-limited disease</b>		<b>0.012</b>
No (N=307)	428 (262-856)	
Yes (N=131)	341 (198-635)	
<b>Synchronous metastases</b>		<b>0.001</b>
No (N=97)	317 (211-522)	
Yes (N=341)	442 (262-835)	
<b>Number of metastatic sites</b>		<b>0.002</b>
1 (N=181)	347 (212-623)	
> 1 (N=257)	441 (273-1005)	
<b>Primary tumour sidedness</b>		0.295
Left (N=330)	398 (234-773)	
Right (N=108)	452 (270-828)	
<b>RAS/BRAF status</b>		0.395
RAS/BRAF wild-type (N=276)	420 (245-814)	
RAS mutated (N=146)	376 (226-740)	
BRAF mutated (N=16)	602 (268-1056)	
<b>Study</b>		0.565
Valentino (N=207)	421 (252-814)	
TRIBE (N=231)	400 (237-774)	
<b>Chemotherapy Backbone</b>		0.838
Doublet (N=321)	415 (239-796)	
Triplet (N=117)	429 (248-748)	
* Mann–Whitney test or Kruskal-Wallis test, as appropriate		
Abbreviations. IQR: interquartile range; ECOG: Eastern Cooperative Oncology Group; PS: performance status; PIV: Pan-immune Inflammation Value.		

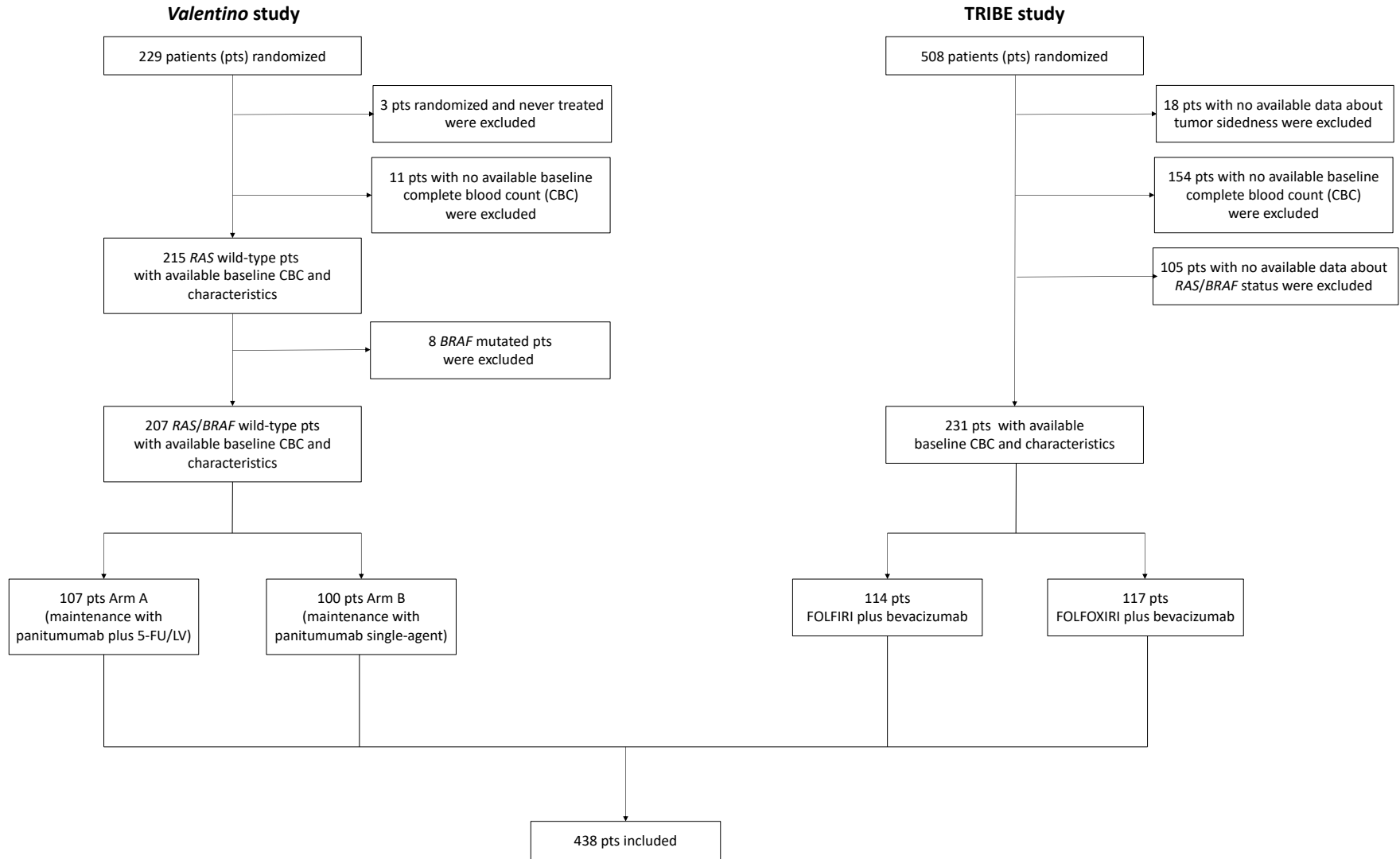
**Supplementary Table S3. Association between PIV and classic immune-inflammatory biomarkers.**

Characteristics	Total (N=438) N (%)	PIV low (N=208) N (%)	PIV high (N=230) N (%)	P*
<b>NLR</b>				<b>&lt;0.001</b>
Low	251 (57)	177 (85)	74 (32)	
High	187 (43)	31 (15)	156 (68)	
<b>PLT</b>				<b>&lt;0.001</b>
Low	264 (60)	177 (85)	87 (38)	
High	174 (40)	31 (15)	143 (62)	
<b>MONO</b>				<b>&lt;0.001</b>
Low	193 (44)	147 (71)	46 (20)	
High	245 (56)	61 (29)	184 (80)	
<b>SII</b>				<b>&lt;0.001</b>
Low	206 (47)	173 (83)	33 (14)	
High	232 (53)	35 (17)	197 (86)	
* Fisher exact test or Chi square test as appropriate				
<i>Abbreviations.</i> IQR: interquartile range; PIV: Pan-immune-Inflammation Value; NLR: neutrophil-to-lymphocyte ration; PLR: platelet count; MONO: monocyte count; SII: systemic immune-inflammation index.				

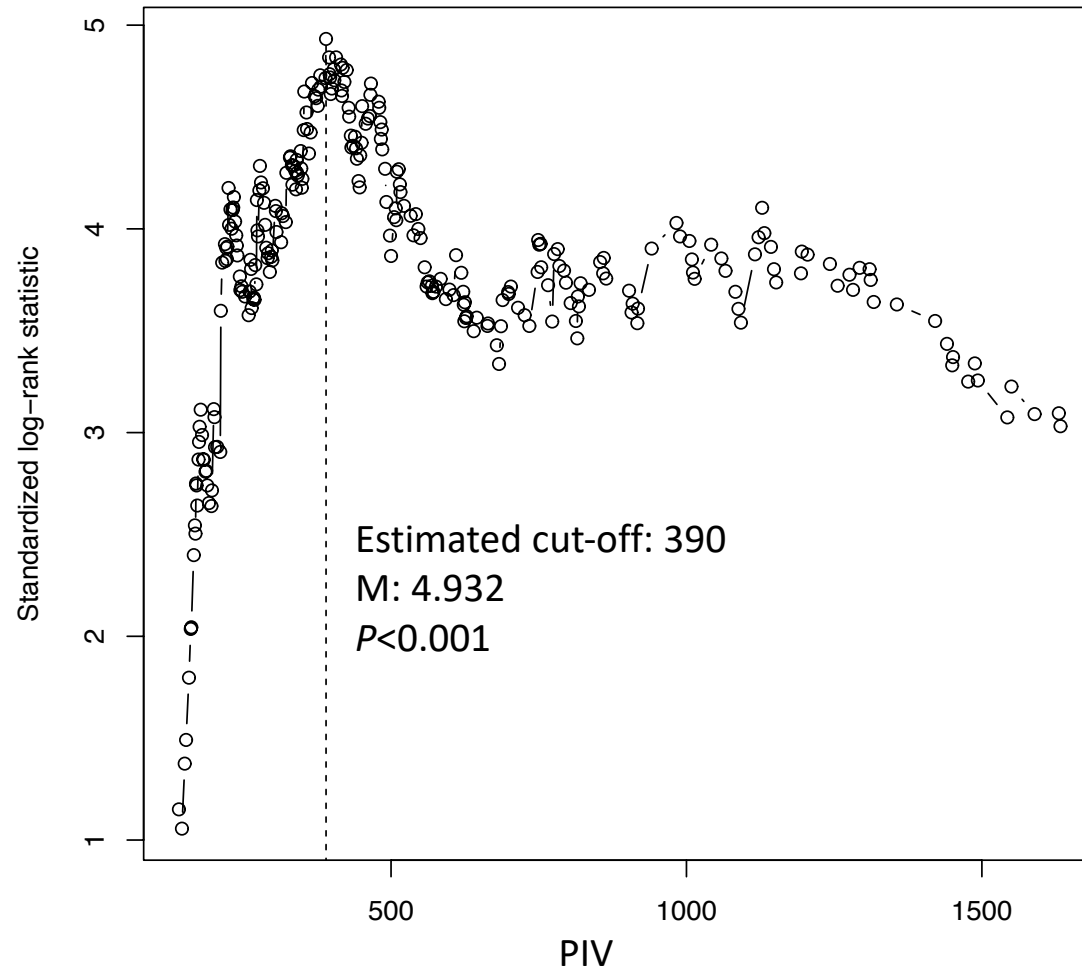
**Supplementary Table S4. Predictive analyses according to PIV in the *Valentino* and TRIBE studies.**

<b>Valentino study</b>							
<b>Outcomes</b>	<b>Arm A</b>	<b>Low PIV Arm B</b>	<b>HR (95% CI)</b>	<b>Arm A</b>	<b>High PIV Arm B</b>	<b>HR (95% CI)</b>	<b>Interaction test <i>P</i></b>
Median PFS, months (95% CI)	17.2 (12.9-22.9)	12.2 (9.9-15.4)	1.61 (1.01-2.58)	10.5 (8.8-14.6)	8.9 (7.5-10.9)	1.26 (0.85-1.86)	0.449
Median OS, months (95% CI)	NA (28.3-NA)	NA (32.5-NA)	0.94 (0.44-2.00)	24.2 (17.8-31.1)	22.1 (16.6-NA)	1.15 (0.71-1.86)	0.612
<b>TRIBE study</b>							
<b>Outcomes</b>	<b>Doublet</b>	<b>Low PIV Triplet</b>	<b>HR (95% CI)</b>	<b>Doublet</b>	<b>High PIV Triplet</b>	<b>HR (95% CI)</b>	<b>Interaction test <i>P</i></b>
Median PFS, months (95% CI)	10.9 (9.2-14.6)	13.2 (12.1-18.2)	0.83 (0.56-1.23)	8.7 (7.8-11.3)	9.6 (8.4-13.1)	0.83 (0.57-1.20)	0.924
Median OS, months (95% CI)	31.6 (25.1-42.7)	33.9 (31.0-44.2)	0.93 (0.59-1.45)	20.6 (18.4-31.4)	23.4 (19.6-30.8)	0.94 (0.63-1.41)	0.951
<i>Abbreviations:</i> PIV: Pan-immune-Inflammation Value; PFS: progression-free survival; OS: overall survival; HR: hazard ratio.							

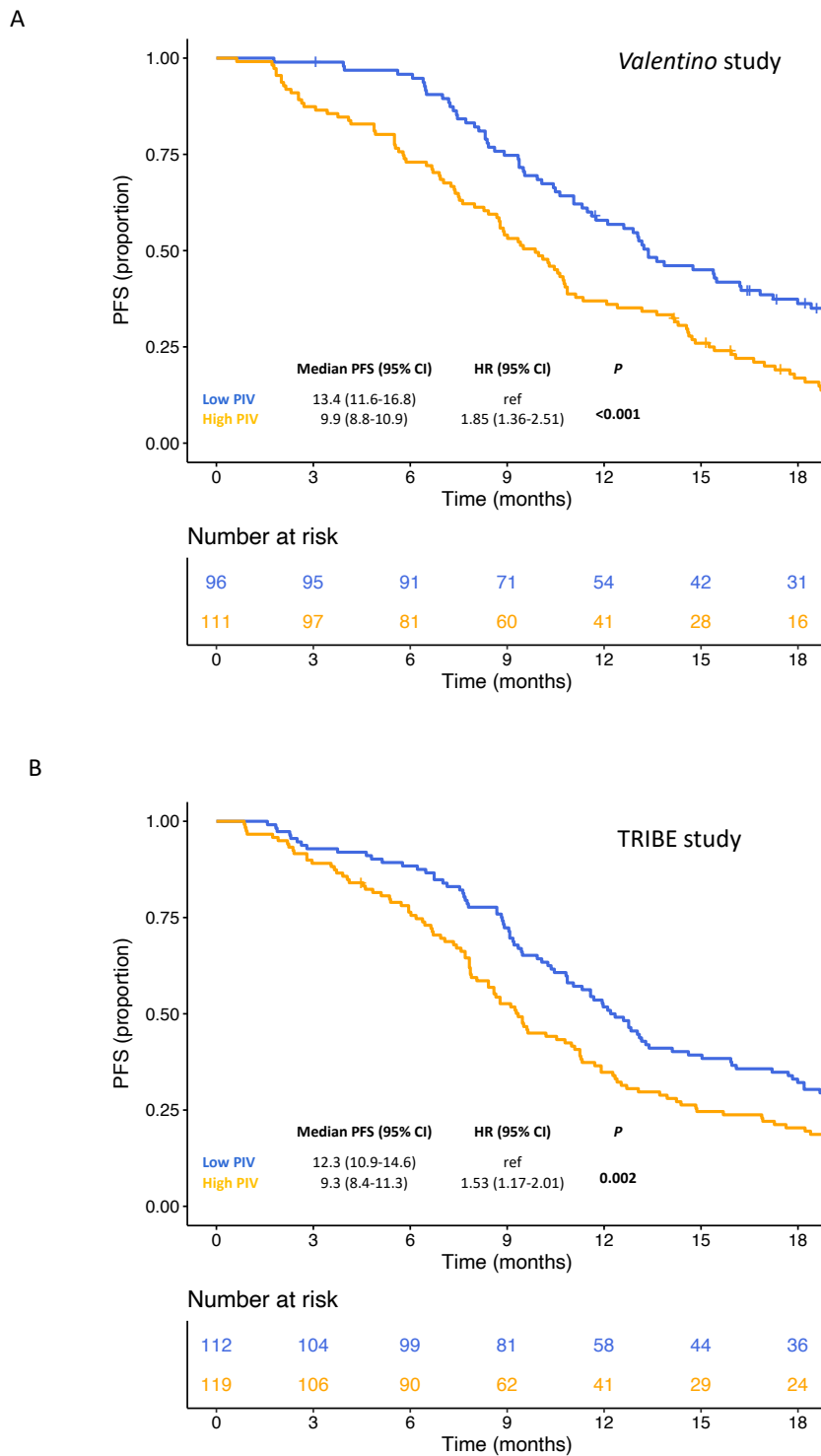
**Supplementary Figure S1. Flow chart showing the process of patients' selection.**



**Supplementary Figure S2. Dot plot showing the standardized log-rank test statistic for PFS according to PIV value. The best cut-off value for PIV was 390, with a standardized log-rank test statistic (M) of 4.932.**



**Supplementary Figure S3. Kaplan-Meier curve for PFS according to PIV in the Valentino (panel A) and TRIBE (panel B) study populations.** Blue lines indicate patients with low PIV whereas yellow lines indicate patients with high PIV. Patients with high PIV had worse PFS respect to patients with low PIV regardless of the study.



**Supplementary Figure S4. Kaplan-Meier curve for OS according to PIV in the Valentino**

**(panel A) and TRIBE (panel B) study populations.** Blue lines indicate patients with low PIV whereas yellow lines indicate patients with high PIV. Patients with high PIV had worse OS respect to patients with low PIV regardless of the study.

