Association of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio with clinical outcomes to tislelizumab monotherapy in patients with previously treated advanced hepatocellular carcinoma

Authors:

Philippe Merle,[1] Helena Verdaguer Mata,[2] Congying Xie,[3] Richard Hubner,[4] Yong Liu,[5] Jane Margetts,[6] Ying Cheng,[7] Yee Chao,[8] Cong Fei,[9] Chen Ling,[9] Ruiqi Huang,[9] Xikun Wu,[9] Zhirong Shen,[10] Bai Li, [10] Sandra Chica Duque,[11] Zhenggang Ren[12]

Affiliations: [1]Hepatology and Gastroenterology Unit, Hospital La Croix-Rousse, Lyon, France; [2]Department of Medical Oncology, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [3]Department of Radiation and Medical Oncology, Second Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; [4]Medical Oncology Department, The Christie NHS Foundation Trust, Manchester, UK; [5]Department of Oncology, Xuzhou Central Hosptial, School of Medicine, Southeast University, Xuzhou, China; [6]Northern Centre for Cancer Care, Newcastle-upon-Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK; [7]Department of Medical Oncology, Jilin Cancer Hospital, Changchun, China; [8]Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan; [9] BeiGene (Shanghai) Co., Ltd., Shanghai, China; [10]BeiGene (Beijing) Co., Ltd., Beijing, China; [11]BeiGene (San Mateo) Co., Ltd., San Mateo, CA, USA; [12]Department of Hepatic Oncology, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China.

Background:

Tislelizumab, an anti-PD-1 monoclonal antibody, demonstrated clinical activity and was well-tolerated in patients with previously treated advanced hepatocellular carcinoma (HCC) in the Phase 2 RATIONALE-208 study (NCT03419897). We explored whether baseline neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) or their post-treatment change correlated with clinical efficacy of tislelizumab treatment.

Methods:

Eligible patients (>18 years) who had received ≥1 prior line of systemic therapy for advanced HCC were administered open-label tislelizumab (200 mg) intravenously every 3 weeks until no further clinical benefit was observed. NLR and PLR were assessed using peripheral blood samples collected at baseline, Cycle 2 Day 1 (C2D1), C3D1, and C4D1. Survival analysis (progression free survival [PFS] and overall survival [OS]) was conducted by Kaplan-Meier method and survival rate at risk was compared by log rank test. Logistic regression was used to analyze association of post-treatment change of NLR or PLR with objective response rate (ORR). In the baseline analysis, median NLR or PLR in this study was used as a cut-off. All statistical analysis results are post-hoc exploratory and thereby p values are descriptive.

Results:

Overall, 249 patients were enrolled, of which 249, 234, 203, and 186 patients had evaluable NLR and PLR data at baseline, C2D1, C3D1, and C4D1, respectively. Analysis of NLR at baseline, using median NLR (3.2) as cut-off, demonstrated higher OS (p=0.0024) and PFS (p=0.071) in NLR-low versus NLR-high groups (median OS [mOS]:17.4 versus 9.9 months; median PFS [mPFS]: 2.8 versus 1.5 months). Analysis of PLR at baseline, using median PLR (141.4) as cut-off, showed higher OS (p=0.0085) and PFS (p<0.0001) in PLR-low versus PLR-high groups (mOS: 16.2 versus 10.8 months; mPFS: 2.8 versus 1.4 months). In post-treatment analysis, patients with decreased NLR or PLR at C2D1, C3D1 or C4D1 had higher ORR **(Table 1)** and longer OS **(Figure 1)** compared with patients with increased NLR or PLR at each timepoint.

Conclusions:

In patients with previously treated advanced HCC that received tislelizumab monotherapy, lower baseline NLR or PLR was associated with longer OS and PFS, and post-treatment decreases of NLR or PLR were associated with higher ORR and longer OS. These observations support NLR and PLR as potential prognostic biomarkers in patients with advanced HCC treated with tislelizumab and will be further investigated in an on-going Phase 3 study (NCT03412773).

Figures/tables:

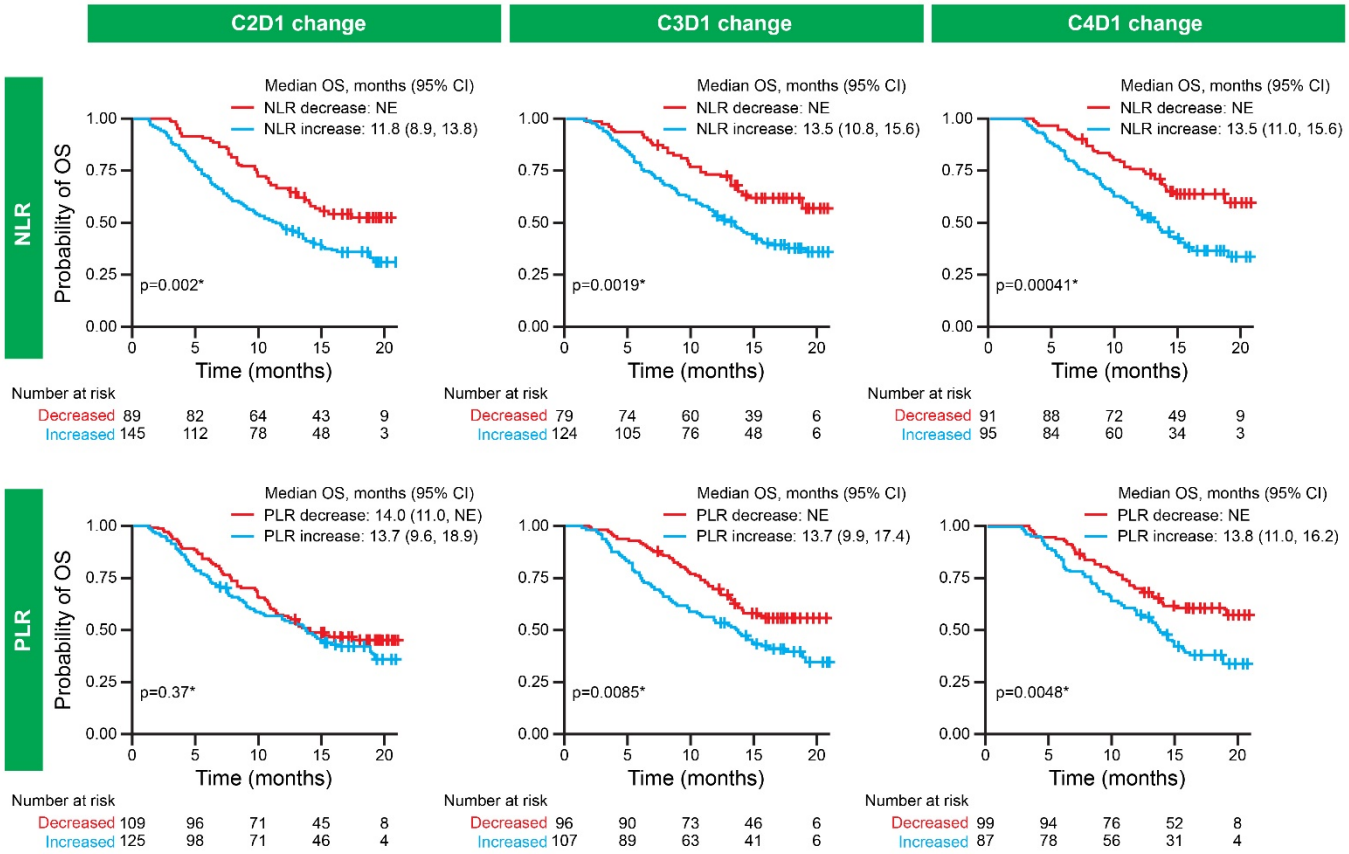
Table 1. Post-treatment decreases in NLR or PLR were associated with response to tislelizumab monotherapy

	C2D1 change		C3D1 change		C4D1 change	
NLR	**Decreased (N=89)**	**Increased (N=145)**	**Decreased (N=79)**	**Increased (N=124)**	**Decreased (N=91)**	**Increased (N=95)**
ORR	22%	8%	27%	9%	26%	7%
OR (95% CI), p value*	0.31 (0.14, 0.67) 0.0031		0.28 (0.12, 0.61) 0.0015		0.22 (0.09, 0.55) 0.0011	
PLR	**Decreased (N=109)**	**Increased (N=125)**	**Decreased (N=96)**	**Increased (N=107)**	**Decreased (N=99)**	**Increased (N=87)**
ORR	19%	10%	25%	8%	27%	5%
OR (95% CI), p value*	0.47 (0.22, 1.02) 0.0556		0.24 (0.10, 0.57) 0.0012		0.13 (0.04, 0.38) 0.0002	

*Determined by logistic regression

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CXDX, Cycle X Day X; ORR, objective response rate; OR, odds ratio; CI, confidence interval

Figure 1. Post-treatment decreases in NLR or PLR were associated with improved OS following tislelizumab monotherapy



*p value determined by log rank test to compare the survival rate at risk
NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CXDX, Cycle X Day X; OS, overall survival; NE, not evaluable; CI, confidence interval