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

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Introduction

- Tislelizumab is an anti-programmed death protein-1 (PD-1) antibody that has high affinity and binding specificity for PD-1[1–3]
- Tislelizumab demonstrated clinical activity and was generally well tolerated in patients with previously treated advanced hepatocellular carcinoma (HCC) in the open-label, multicenter, Phase 2 RATIONALE-208 study (NCT03419897)[4]
  - After a median follow-up of 12.4 months (data cut-off: February 2020):[4]
    - Objective response rate (ORR) was 13.3% (95% CI: 9.3, 18.1)
    - Median progression-free survival (PFS) was 2.7 months (95% CI: 1.4, 2.8)
    - Median overall survival (OS) was 13.2 months (95% CI: 10.8, 15.0)
- Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been proposed as potential prognostic biomarkers for clinical outcomes during anti-PD-1 therapy in a variety of tumor types, including HCC[5,6]
- We explored whether baseline NLR and PLR, or NLR and PLR changes from baseline, correlated with the clinical efficacy of tislelizumab in the RATIONALE-208 study

Methods

RATIONALE 208 study design

- Study design has been previously described; scan QR code to read full study methods:

NLR and PLR assessment

- Neutrophil, platelet, and lymphocyte levels were assessed using blood samples collected at baseline and on Day 1 of Cycles 2, 3 and 4

Analysis of association between NLR, PLR, and clinical outcomes

- Analyses were performed using the biomarker evaluable population at each timepoint
  - Biomarker evaluable population included all patients receiving ≥ 1 dose of tislelizumab who had evaluable biomarker data at the respective timepoint
- Distributions of OS and PFS for each subgroup were estimated by the Kaplan–Meier method and compared by means of log-rank tests
- For analysis of the association between baseline biomarker levels and outcomes, median NLR and PLR were used as a cut-off for defining 'high' and 'low' subgroups
- Logistic regression was used to analyze the association of NLR or PLR changes from baseline with ORR
- All statistical analysis results are *post-hoc* exploratory and thereby p values are descriptive

Results

Patient characteristics and clinical outcomes

- As of February 2020, 249 patients were enrolled and received ≥ 1 dose of tislelizumab
- Demographics and characteristics were similar in the biomarker evaluable populations at each assessment timepoint (**Table 1**)

Table 1. Characteristics and clinical outcomes of biomarker evaluable population at specified timepoints

Characteristic	C1D1 (n=249)	C2D1 (n=234)	C3D1 (n=203)	C4D1 (n=186)
Male, n (%)	217 (87.1)	204 (87.2)	180 (88.7)	164 (88.2)
Age, n (%)				
< 65 years	149 (59.8)	142 (60.7)	121 (59.6)	106 (57.0)
≥ 65 years	100 (40.2)	92 (39.3)	82 (40.4)	80 (43.0)
Region, n (%)				
Mainland China and Taiwan	122 (49.0)	117 (50.0)	95 (46.8)	83 (44.6)
Europe	127 (51.0)	117 (50.0)	108 (53.2)	103 (55.4)
ECOG PS status, n (%)				
0	129 (51.8)	124 (53.0)	108 (53.2)	98 (52.7)
1	120 (48.2)	110 (47.0)	95 (46.8)	88 (47.3)
Prior lines of therapy, n (%)				
1	138 (55.4)	126 (53.8)	110 (54.2)	97 (52.2)
≥ 2	111 (44.6)	108 (46.2)	93 (45.8)	89 (47.8)
HCC etiology, n (%)				
Hepatitis B	128 (51.4)	122 (52.1)	102 (50.2)	89 (47.8)
Hepatitis C	31 (12.4)	29 (12.4)	25 (12.3)	24 (12.9)
Non-viral	90 (36.1)	83 (35.5)	76 (37.4)	73 (39.2)
Clinical outcome				
ORR*, n (%)	33 (13.3)	32 (13.7)	32 (15.8)	31 (16.7)
Median PFS*, months (95% CI)	2.7 (1.5, 2.8)	2.7 (1.6, 2.8)	2.8 (2.7, 2.9)	2.8 (2.7, 4.1)
Median OS, months (95% CI)	13.2 (10.8, 15.0)	13.7 (11.8, 16.2)	15.2 (13.5, NE)	16.2 (13.8, NE)

IRC-assessed; CI, confidence interval; CXDX, cycle X, day X; ECOG PS, Eastern Cooperative Oncology Group performance score; HCC, hepatocellular carcinoma; IRC, independent review committee; NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

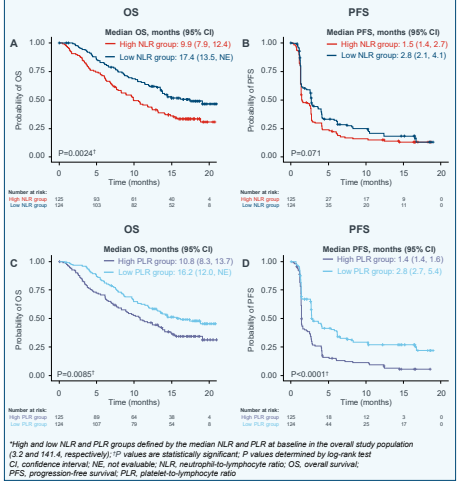
Association between baseline NLR or PLR and outcomes

- Median NLR and PLR at baseline (C1D1) in the overall study population were 3.2 and 141.4, respectively
- Using the median NLR and PLR as cut-offs for defining 'high' and 'low' groups:
  - The low NLR group had significantly longer OS and a trend toward longer PFS compared with the high NLR group (**Figure 1A, B**)
  - The low PLR group had significantly longer OS and PFS compared with the high PLR group (**Figure 1C, D**)

Association between NLR or PLR changes from baseline and response to tislelizumab

- ORR was higher in patients with decreased NLR or PLR from baseline at C2D1, C3D1, or C4D1 compared with those with increased or unchanged biomarker levels (**Figure 2**)

Figure 1. Association between baseline NLR or PLR and survival outcomes*



High and low NLR and PLR groups defined by the median NLR and PLR at baseline in the overall study population (3.2 and 141.4, respectively);†P values are statistically significant; P values determined by log-rank test
CI, confidence interval; NE, not evaluable; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PFS, progression-free survival; PLR, platelet-to-lymphocyte ratio

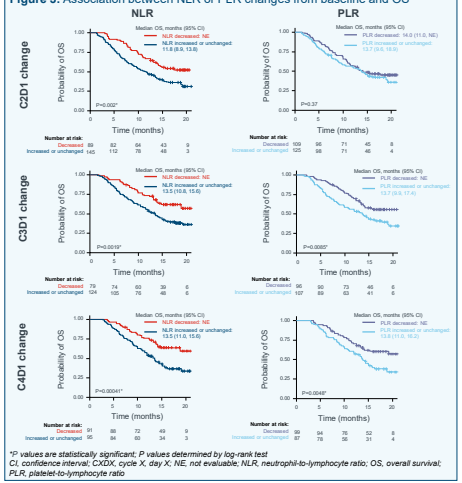
Figure 2. Association between change in NLR or PLR from baseline and ORR

Biomarker	Time-point	NLR or PLR decreased n	NLR or PLR decreased ORR, %	NLR or PLR increased or unchanged n	NLR or PLR increased or unchanged ORR, %	OR (95% CI) for response to TIS for increased or unchanged vs decreased	P value
NLR	C2D1	89	22	145	8		0.0031*
	C3D1	79	27	124	9		0.0015*
	C4D1	91	26	95	7		0.0011*
PLR	C2D1	109	19	125	10		0.0556
	C3D1	96	25	107	8		0.0012*
	C4D1	99	27	87	5		0.0002*

0.1 0.3 1.0

**P values are statistically significant; P values determined by logistic regression*
CI, confidence interval; CXDX, cycle X, day X; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; ORR, objective response rate; PLR, platelet-to-lymphocyte ratio; TIS, tislelizumab

Figure 3. Association between NLR or PLR changes from baseline and OS



**P values are statistically significant; P values determined by log-rank test*
CI, confidence interval; CXDX, cycle X, day X; NE, not evaluable; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PLR, platelet-to-lymphocyte ratio

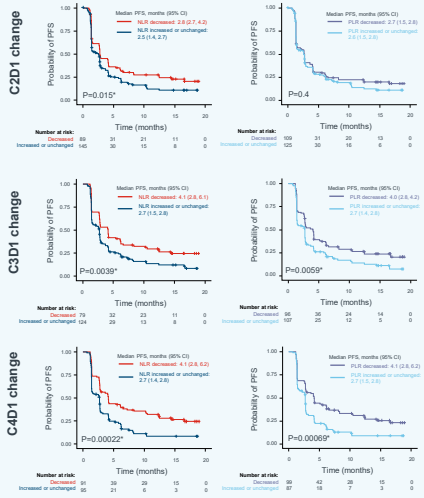
Conclusions

- In patients with previously treated advanced HCC who received tislelizumab monotherapy in the Phase 2 RATIONALE-208 study:
  - Lower NLR or PLR at baseline was associated with longer OS and PFS compared with higher NLR or PLR at baseline
  - Decreased NLR or PLR from baseline was associated with higher ORR and longer OS and PFS compared with increased or unchanged NLR or PLR from baseline
- These observations support NLR and PLR as potential prognostic biomarkers in patients with advanced HCC treated with tislelizumab
- Further investigation of these biomarkers will be conducted in an ongoing randomized Phase 3 study of tislelizumab vs sorafenib as first-line therapy in patients with advanced HCC (NCT03412773)

Association between NLR or PLR changes from baseline and survival

- Decreased NLR or PLR from baseline at C2D1, C3D1, or C4D1 was associated with longer OS, compared with increased or unchanged NLR or PLR from baseline (**Figure 3**)
- Decreased NLR or PLR from baseline at C2D1, C3D1, or C4D1 was associated with longer PFS, compared with increased or unchanged NLR or PLR from baseline (**Figure 4**)

Figure 4. Association between NLR or PLR changes from baseline and PFS



**P values are statistically significant; P values determined by log-rank test*
CI, confidence interval; CXDX, cycle X, day X; NLR, neutrophil-to-lymphocyte ratio; PFS, progression-free survival; PLR, platelet-to-lymphocyte ratio

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