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Neutrophil-to-Lymphocyte Ratio Predicts Immune-related Adverse Events in Patients With Hepatocellular Carcinoma Treated With Atezolizumab Plus Bevacizumab

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Abstract. *Background/Aim: Atezolizumab in combination with bevacizumab is an approved systemic chemotherapy regimen for advanced hepatocellular carcinoma (HCC). However, immune checkpoint inhibitors (ICIs), such as atezolizumab, frequently lead to immune-related adverse events (irAEs). The identification of biomarkers that can predict the occurrence of irAEs is crucial for the optimal management of patients undergoing ICI treatment. Patients and Methods: Between October 2020 and June 2023, we conducted a study involving 69 patients with advanced HCC who received treatment with atezolizumab plus bevacizumab. We conducted an analysis of blood-based biomarkers to identify independent risk factors associated with irAEs. Results: In our study, 12 out of 69 patients (17.4%) experienced irAEs. Our investigation into blood-based biomarkers revealed that a neutrophil–to-lymphocyte ratio (NLR) <2.04 at three weeks after the initiation of treatment had high predictive power (area under the curve: 0.77) for irAEs. Furthermore, multivariate logistic analysis identified NLR at three weeks (hazard ratio=0.23; p=0.037) and non-viral infection (hazard ratio=4.47; p=0.037) as independent factors contributing to the occurrence of irAEs. Patients who developed irAEs demonstrated a more favorable overall response rate (75.0% vs. 28.1%, p=0.005), disease control rate (91.6% vs. 52.6%, p=0.016), and progression-free survival (12.1 months vs. 6.0 months, p=0.010) than those who did not experience irAEs. Conclusion: An NLR <2.04 at three weeks after the initiation of treatment may serve as a valuable biomarker for predicting irAEs in patients with HCC undergoing atezolizumab plus bevacizumab therapy.*

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Hepatocellular carcinoma (HCC) is the sixth most prevalent neoplasm and causes the third most cancer-related fatalities globally, accounting for an estimated 900,000 new cases and 830,000 deaths in 2020 (1, 2). Recent advancements in systemic chemotherapy for advanced HCC, including the development of immune checkpoint inhibitors (ICIs) and molecular targeted agents, have markedly enhanced patient outcomes (3-7).

The IMbrave150 study demonstrated the efficacy of atezolizumab plus bevacizumab, monoclonal antibodies targeting programmed death ligand 1 (PD-L1) and vascular endothelial growth factor (VEGF), respectively. This combination therapy led to extended progression-free survival (PFS) and overall survival (OS) in comparison to sorafenib for patients with advanced HCC (3). Consequently, atezolizumab plus bevacizumab is emerging as the primary systemic chemotherapy for advanced HCC.

ICIs stimulate an intensified T-cell-mediated response to facilitate the eradication of tumor cells. However, this heightened immune activity can also provoke a broad spectrum of adverse effects termed immune-related adverse events (irAEs). These irAEs can impact diverse organs, including the skin, gastrointestinal tract, liver, respiratory system, thyroid, and pituitary glands (8). The importance of irAEs is substantial as they are prevalent and often cause severe complications that can profoundly affect the quality of life and prognosis of patients undergoing ICI therapy. Moreover, finding the optimal approach to manage irAEs without compromising the antitumor response and long-term survival remains a challenge (9). Interestingly, patients experiencing irAEs tend to have a more favorable cancer-related prognosis (10-12). Thus, evaluating the individual risk of toxicity in advance is pivotal to guide the early management of irAEs. This proactive approach can enable the continued administration of ICIs to

Table I. *Baseline characteristics of patients who received atezolizumab plus bevacizumab.*

Characteristics	All	irAE	Non-irAE	*p*-Value
Number	69	12	57	
Age, years	73 (65.5-79.5)	76.5 (71.5-81.8)	72 (64.0-78.5)	0.202
Sex, n (male/female)	57/12	10/2	47/10	0.942
BMI (kg/m^2)	23.4 (21.3-25.9)	24.6 (21.5-26.5)	23.4 (21.1-25.8)	0.545
MVI positive, n	20	1	19	0.057
EHS positive, n	18	5	13	0.193
intrahepatic max tumor size, cm	4.0 (2.4-6.9)	4.4 (1.3-7.3)	4.0 (2.5-6.8)	0.682
Numbers of tumors >5	41	5	36	0.293
Etiology				0.033
HBV	12	1	10	
HCV	30	3	28	
Non-viral	27	8	19	
Child-Pugh				0.328
Child-Pugh score A	57	11	46	
Child-Pugh score B/C	12	1	11	
Alb, g/dl	3.7 (3.3-4.1)	3.8 (3.6-4.2)	3.6 (3.3-4.1)	0.154
T.Bil, g/dl	0.9 (0.6-1.2)	1.1 (0.6-1.3)	0.9 (0.6-1.2)	0.868
ALBI score	–2.39 (–2.71- –2.05)	–2.43 (–2.75- –2.26)	–2.36 (–2.71- –2.02)	0.222
BCLC stage				0.139
A	3	2	1	
B	30	4	26	
C	36	6	30	
Tumor marker				
AFP, ng/ml	45.7 (6.0-781.7)	30.2 (3.4-491.9)	52.5 (7.3-955.2)	0.607
PIVKA-II, mAU/ml	428.0 (59.5-3,170.5)	287.5 (65.3-1,032.8)	546.0 (55.0-4,631.0)	0.786
FBC data (SOT)				
Neutrophil (/μl)	2,867.5 (2,255.5-3,795.1)	2,997.9 (2,443.9-3,061.0)	2,859.8 (2,189.4-3,958.2)	0.509
Lymphocyte (/μl)	1,207.7 (828.7-1,594.9)	1,291.5 (879.9-1,558.9)	1,203.8 (804.8-1,628.9)	0.869
Eosinophil (/μl)	136.2 (91.0-276.3)	121.9 (86.9-307.4)	136.2 (91.0-276.3)	0.769
Platelet (×10^4/μl)	14.8 (9.7-18.5)	14.5 (9.9-18.3)	14.8 (9.2-19.0)	0.882
NLR (SOT)	2.69 (2.38-2.95)	2.69 (2.34-2.78)	2.66 (2.38-2.97)	0.596
PLR (SOT)	118.9 (88.5-152.7)	120.8 (94.3-152.9)	118.2 (86.6-152.7)	0.548
FBC data (Week 3)				
Neutrophil (/μl)	3,273.8 (2,135.0-3,962.1)	2,404.3 (1,680.6-3,513.5)	3,384.5 (2,268.5-4,204.4)	0.135
Lymphocyte (/μl)	1,263.9 (813.4-1,813.5)	1,449.2 (1,109.9-1,888.6)	1,254.9 (758.7-1,743.1)	0.193
Eosinophil (/μl)	157.9 (80.8-279.3)	224.7 (115.4-393.2)	153.7 (76.2-251.0)	0.687
Platelet (×10^4/μl)	16.1 (10.1-19.3)	16.1 (12.4-18.5)	17.7 (9.7-20.9)	0.707
NLR (Week 3)	2.29 (1.76-3.76)	1.85 (1.18-2.34)	2.63 (1.79-3.82)	0.019
PLR (Week 3)	121.5 (85.9-174.8)	103.3 (77.4-144.4)	131.8 (888.3-185.9)	0.159

Data are expressed as median (interquartile range). irAE: Immune-related adverse event; BMI: Body Mass Index; HBV: hepatitis B virus; HCV: hepatitis C virus; MVI: microvascular invasion; EHS: extrahepatic spread; Alb: albumin; T.Bil: total bilirubin; ALBI score: albumin-bilirubin score; BCLC stage: Barcelona Clinic liver cancer stage; AFP: α-fetoprotein; PIVKA-II: vitamin K absence or antagonist-II; FBC: full blood count; SOT: start of treatment; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.

patients who are vulnerable to immune-mediated complications and, paradoxically, allow them to benefit more from treatment. As the use of ICIs continues to expand in the field of oncology, there is a growing need for dependable and validated biomarkers capable of predicting irAEs.

Regrettably, our understanding of predictive factors for irAEs in patients with HCC is limited. Therefore, we initiated an investigation to identify predictive factors for irAEs in patients with HCC undergoing treatment with atezolizumab plus bevacizumab.

Patients and Methods

Patients. In this single-center, prospective study conducted at the Aso Iizuka Hospital from December 2020 to June 2023, we enrolled patients with HCC who were administered atezolizumab plus bevacizumab. Of the 84 patients treated, 15 with a follow-up duration of less than 12 weeks were excluded, leaving 69 patients for evaluation. This study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Aso Iizuka Hospital (approval No. 22008). The opt-out method was used to obtain consent for this study.

Table II. *The area under the receiver operating characteristic (AUROC) value of parameters associated with immune-related adverse event (irAE) occurrence.*

	AUC	1-Specificity	Sensitivity	Cut-off value
SOT				
Neutrophil (/μl)	0.512	0.561	0.833	3,077.8
Lymphocyte (/μl)	0.539	0.737	0.917	824.4
Eosinophil (/μl)	0.531	0.281	0.500	95.0
NLR	0.542	0.544	0.833	2.80
PLR	0.505	0.772	0.917	156.4
Week 3				
Neutrophil (/μl)	0.642	0.281	0.583	2,460.2
Lymphocyte (/μl)	0.646	0.614	0.917	1,062.3
Eosinophil (/μl)	0.633	0.211	0.500	2.04
NLR (Week 3)	0.746	0.351	0.750	2.04
PLR (Week 3)	0.629	0.597	0.917	156.8

SOT: Start of treatment; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; AUC: area under the curve.

Definition of irAEs. Adverse events perceived to have a possible immunological root, necessitating enhanced surveillance and potential intervention with immune suppressants or endocrine therapies, were categorized as irAEs. They were rated based on the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).

Biomarker analysis. The neutrophil–to-lymphocyte ratio (NLR) was determined by the quotient of the total neutrophils to total lymphocytes in peripheral blood, whereas the platelet-to-lymphocyte ratio (PLR) was ascertained by dividing the total platelets by the total lymphocytes.

Treatment protocol. Following the IMbrave150 trial protocol (3), patients were intravenously administered atezolizumab (1,200 mg) and bevacizumab (7.5 mg/kg) from Chugai (Tokyo, Japan) every three weeks. Treatment persisted until disease aggravation (PD) or the emergence of insufferable adverse events.

Evaluation of efficacy. Every 6 to 12 weeks following the start of treatment, computed tomography or magnetic resonance imaging were used to assess the treatment response. The antitumor response was gauged using modified RECIST version 1.1 (13). Indications of disease control rate (DCR) included complete response (CR), partial response (PR), and stable disease (SD) that persisted for a minimum of four months. The summation of PR and CR defined the objective response rate (ORR). Every three weeks, patients underwent evaluations and received treatment until either disease escalation (PD) or adverse reactions became intolerable.

Definitions of viral and non-viral infection. Patients with either anti-HCV antibody (Ab) or HBs-antigen (Ag) presence were classified as having a viral infection. Conversely, those negative for both serum anti-HCV Ab and HBs-Ag were categorized as having non-viral infections.

Statistical analysis. For all data processing, JMP Pro version 11 (SAS Institute, Cary, NC, USA) was used. The data are presented as median values with interquartile ranges. The Kaplan-Meier method, log-rank test, receiver operating characteristic (ROC) analysis, and Cox hazard analysis were the statistical tests applied. To determine predictive factors for irAE manifestation, ROC and area under the curve (AUC) values were computed. Differences in groups were assessed using the chi-squared test. All *p*-values were derived from two-tailed tests, and $p<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. The characteristics of the 69 patients who received atezolizumab plus bevacizumab are shown in Table I. Twelve patients (17.4%) experienced grade >2 irAEs, which included five cases of adrenal insufficiency, two cases of interstitial pneumonia, two cases of tubulointerstitial nephritis, one case of enterocolitis, one case of stomatitis, and one case of immune thrombocytopenia. We classified the enrolled patients into those who experienced irAEs (irAE group) and those who did not (non-irAE group). The median age of the entire cohort was 73.0 (65.5-72.5) years old, and 82.6% of the patients were male. There were 12, 30, and 27 patients categorized as HBs-Ag, HCV Ab, and non-viral, respectively. In the irAE group, two patients had disease in Barcelona Clinic Liver Cancer (BCLC) stage A, four in BCLC stage B, and six in BCLC stage C. In the non-irAE group, one patient had disease in BCLC stage A, 26 in BCLC stage B, and 33 in BCLC stage C. Age, sex, body mass index, Child–Pugh grade, albumin-bilirubin score (ALBI) score, tumor size, number of intrahepatic lesions, microvascular invasion, extrahepatic spread, serum α-fetoprotein levels, protein induced by vitamin K absence or antagonist-II (known as PIVKA-II) levels, and NLR were similar between the two groups at the start of treatment. At three weeks after the start of treatment, patients in the irAE group had a lower NLR than those in the non-irAE group ($p=0.019$). There were more non-viral patients in the irAE group than in the non-irAE group ($p=0.033$).

Table III. *Factors associated with immune-related adverse events.*

	Univariate			Multivariate		
Predictor	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Sex	1.064	0.200-5.620	0.942			
Age	1.043	0.977-1.111	0.183			
BMI	1.062	0.876-1.289	0.538			
NLR (SOT)	0.642	0.127-3.225	0.587			
NLR (Week 3)	0.361	0.152-0.859	0.003	0.223	0.054-0.916	0.037
Non-viral infection	4.000	1.067-14.987	0.033	4.474	1.091-18.34	0.037
ALBI score	0.386	0.083-1.780	0.198			
AFP	0.999	0.999-1.000	0.438			

BMI: Body Mass Index; ALBI score: albumin-bilirubin score; AFP: α-fetoprotein; SOT: start of treatment; NLR: neutrophil-to- lymphocyte ratio.

Table IV. *Comparison of responses to atezolizumab plus bevacizumab between hepatocellular carcinoma in the immune-related adverse events (irAE) and non-irAE groups.*

	All n=69	irAE n=12	Non-irAE n=57	*p*-Value
Overall response				0.004
CR	2	2	0	
PR	23	7	16	
SD	16	2	14	
PD	23	1	22	
NE	5	0	5	
ORR (CR+PR)	24	9	16	0.005
DCR (CR+PR+SD)	41	11	30	0.016

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; NE: not evaluated; ORR: objective response rate; DCR: disease control rate.

Prognostic role of NLR for the development of irAEs. We determined the ROC values for the development of irAEs in the 69 patients based on multiple parameters, and set the cut-off values for the parameters (Table II). The cut-off value for NLR <2.04 at three weeks after the start of treatment was 2.04 (AUC=0.77).

Univariate logistic regression was performed to assess the risk factors for irAEs (Table III). Subsequent multivariate analysis revealed that NLR at three weeks (HR=0.23; p=0.037) and non-viral infection (HR=4.47; p=0.037) were independent factors that may contribute to irAE occurrence (Table III).

Efficacy of the association between irAEs and antitumor response. Among patients who received atezolizumab plus bevacizumab, the ORR (CR+PR) was 9/12 (75.0%) in the irAE group and 15/57 (28.1%) in the non-irAE group (p=0.005). The DCRs (CR+PR+SD) were 11/12 (91.6%) and 30/57 (52.6%) in the irAE and non-irAE groups, respectively (p=0.016) (Table IV). Therefore, there was a higher response rate among patients in the irAE group than in those in the non-irAE group following atezolizumab plus bevacizumab therapy.

Efficacy of the association between irAEs and PFS. The median PFS of all patients who received atezolizumab plus bevacizumab therapy was 6.8 months. Kaplan-Meier analysis revealed that the median PFS in the irAE group (12.1 months) was higher than that in the non-irAE group (6.0 months) (p=0.010) (Figure 1).

Discussion

In patients with advanced HCC, systemic therapy with a blend of ICI and VEGF inhibitors, notably atezolizumab and bevacizumab, is now endorsed (3). Therefore, it is imperative to evaluate irAE risks prior to treatment initiation. Recent research has focused on identifying predictive biomarkers for irAEs (14). The deployment of blood cell metrics for early irAE detection is gaining traction among medical professionals due to its accessibility, cost-efficiency, and straightforward interpretation. Current data, although not

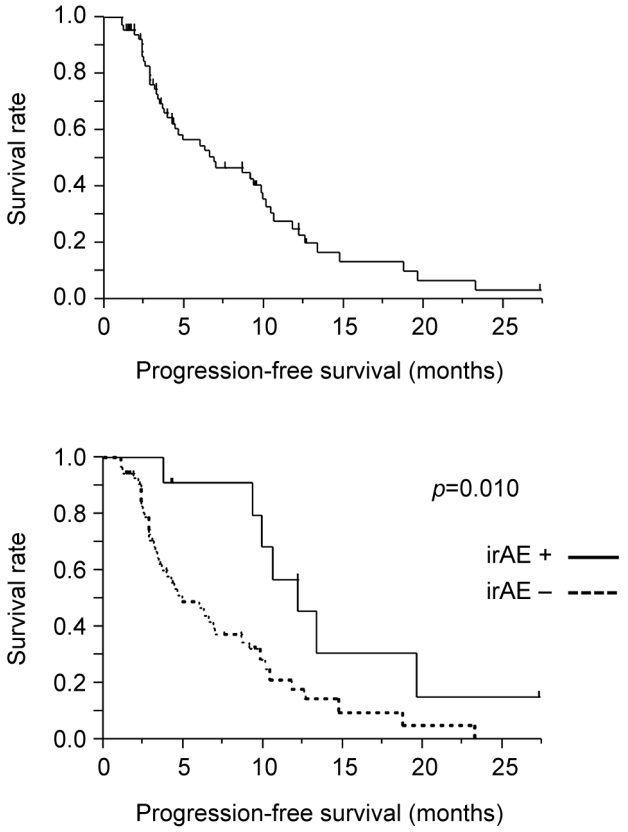

Figure 1. *Kaplan-Meier estimates of progression-free survival (PFS) in patients with hepatocellular carcinoma treated with atezolizumab plus bevacizumab. (A) All patients. (B) Patients in immune-related adverse event (irAE) group and non-irAE group. Significant differences in PFS were determined using the log-rank test. Time 0 was defined as the date of administration of atezolizumab plus bevacizumab.*

uniform, indicate that certain baseline blood cell counts and their increment during monitoring sessions correlate with increased irAE risks (15-34). Remarkably, no prior studies have delved into predictive determinants of irAEs within the HCC demographic. In our research, an NLR<2.04 at three weeks after the start of treatment manifested substantial predictive capability for patients with HCC undergoing atezolizumab and bevacizumab treatment.

The NLR is indicative of the cancer-induced inflammatory reaction and has correlations with patient outcomes and ICI treatment responsiveness across diverse cancer types (35-40). Persano *et al*. reported the prognositc index including NLR in HCC patients being treated with atezolizumab and bevacizumab (41). Eso *et al*. analyzed 40 patients with HCC receiving atezolizumab and bevacizumab and discovered significant NLR discrepancies between different response groups, with the most favorable responses showcasing the lowest NLR values (42). A concurrent multi-institutional study in Japan corroborated these findings, where survival outcomes varied markedly based on NLR levels (43). It has been reported that the NLR did not significantly worsen within 6 weeks after atezolizumab and bevacizumab initiation in HCC patients (44). In our study, Multivariate analysis demonstrated that NLR at three weeks was an independent predictor for OS (data not shown). In summary, NLR at three weeks was considered a vital predictor of irAEs and prognosis.

Recently, several studies have reported that irAEs were associated with the efficacy of ICI therapy in patients with HCC (45). Fukushima *et al*. reported that low-grade irAEs exhibited a strong association with better patient outcomes when treated with atezolizumab and bevacizumab (46). We observed that patients with irAEs had a better ORR and PFS compared to patients without irAEs. Although not statistically significant, OS tended to be longer in the irAE group compared to that in the non-irAE group (22.0 months *vs*. 16.2 months, p=0.10). This result can be attributed to the unmatched liver function at the start of chemotherapy due to the small number of cases.

Interestingly, our study revealed that liver etiology (non-viral) was another predictive marker associated with irAEs. Hatanaka *et al*. reported no significant differences in efficacy, and all treatment-related adverse events, including irAEs, were found between patients with non-viral infection and those with viral infections (47). There have been no previous reports on the association between irAEs and patients with non-viral liver etiology. Nucleoside analogs have been associated with significant improvement in liver inflammation and fibrosis in chronic HBV patients (48). Furthermore, direct-acting antivirals have been shown to reduce fibrosis in chronic HCV patients (49). In our study, most HBV and HCV patients were treated with these drugs, potentially leading to suppressed inflammation. Non-viral patients may have non-viral factors, such as alcohol consumption or obesity, which contribute to pre-existing inflammatory activity and susceptibility to an acute inflammatory response, further heightened by ICIs. More extensive studies are necessary to analyze the relationship between irAEs and liver etiology.

Limitations of this study include the small number of patients with HCC due to its single-center nature. Our results suggest that a lower NLR might enable a more efficient anti-tumor immune response, but also indicate a higher risk of immune-related toxicity.

Conclusion

An NLR <2.04 at three weeks after the start of treatment may be a biomarker for predicting irAEs in patients with HCC treated with atezolizumab plus bevacizumab therapy. Further studies are needed to predict and validate biomarkers for irAEs.

Conflicts of Interest

All Authors declare no competing interests in relation to this study.

Authors' Contributions

A.K., M.Y., A.M., and K.M. designed the study. A.K., Y.K, S.N., K.T., and M.Y. assisted with the data analyses. A.K. wrote the initial draft of the manuscript. M.Y. contributed to the analysis and interpretation of the data. M.Y., A.M., and K.M. assisted in the preparation and critical review of the manuscript. All Authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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References

1 Caldwell S, Park SH: The epidemiology of hepatocellular cancer: from the perspectives of public health problem to tumor biology. J Gastroenterol 44(S19): 96-101, 2009. DOI: 10.1007/s00535-008-2258-6

2 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71(3): 209-249, 2021. DOI: 10.3322/caac.21660

3 Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim T, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu D, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng A: Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 382(20): 1894-1905, 2020. DOI: 10.1056/NEJMoa1915745

4 Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G, Jassem J, Blanc JF, Vogel A, Komov D, Evans TRJ, Lopez C, Dutcus C, Guo M, Saito K, Kraljevic S, Tamai T, Ren M, Cheng AL: Lenvatinib *versus* sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 391(10126): 1163-1173, 2018. DOI: 10.1016/S0140-6736(18)30207-1

5 El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, Kim TY, Choo SP, Trojan J, Welling TH Rd, Meyer T, Kang YK, Yeo W, Chopra A, Anderson J, Dela Cruz C, Lang L, Neely J, Tang H, Dastani HB, Melero I: Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 389(10088): 2492-2502, 2017. DOI: 10.1016/S0140-6736(17)31046-2

6 Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, Verslype C, Zagonel V, Fartoux L, Vogel A, Sarker D, Verset G, Chan SL, Knox J, Daniele B, Webber AL, Ebbinghaus SW, Ma J, Siegel AB, Cheng AL, Kudo M, KEYNOTE-224 investigators: Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): A non-randomised, open-label phase 2 trial. Lancet Oncol 19(7): 940-952, 2018. DOI: 10.1016/S1470-2045(18)30351-6

7 Eso Y, Marusawa H: Novel approaches for molecular targeted therapy against hepatocellular carcinoma. Hepatol Res 48(8): 597-607, 2018. DOI: 10.1111/hepr.13181

8 Postow MA, Sidlow R, Hellmann MD: Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 378(2): 158-168, 2018. DOI: 10.1056/NEJMra1703481

9 Schneider BJ, Naidoo J, Santomasso BD, Lacchetti C, Adkins S, Anadkat M, Atkins MB, Brassil KJ, Caterino JM, Chau I, Davies MJ, Ernstoff MS, Fecher L, Ghosh M, Jaiyesimi I, Mammen JS, Naing A, Nastoupil LJ, Phillips T, Porter LD, Reichner CA, Seigel C, Song JM, Spira A, Suarez-Almazor M, Swami U, Thompson JA, Vikas P, Wang Y, Weber JS, Funchain P, Bollin K: Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO Guideline update. J Clin Oncol 39(36): 4073-4126, 2021. DOI: 10.1200/JCO.21.01440

10 Petrelli F, Grizzi G, Ghidini M, Ghidini A, Ratti M, Panni S, Cabiddu M, Ghilardi M, Borgonovo K, Parati MC, Tomasello G, Barni S, Berruti A, Brighenti M: Immune-related adverse events and survival in solid tumors treated with immune checkpoint inhibitors: a systematic review and meta-analysis. J Immunother 43(1): 1-7, 2020. DOI: 10.1097/CJI.0000000000000300

11 Zhou X, Yao Z, Yang H, Liang N, Zhang X, Zhang F: Are immune-related adverse events associated with the efficacy of immune checkpoint inhibitors in patients with cancer? A systematic review and meta-analysis. BMC Med 18(1): 87, 2020. DOI: 10.1186/s12916-020-01549-2

12 Park R, Lopes L, Saeed A: Anti-PD-1/L1-associated immune-related adverse events as harbinger of favorable clinical outcome: systematic review and meta-analysis. Clin Transl Oncol 23(1): 100-109, 2021. DOI: 10.1007/s12094-020-02397-5

13 Lencioni R, Llovet J: Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 30(01): 052-060, 2010. DOI: 10.1055/s-0030-1247132

14 Les I, Martínez M, Pérez-Francisco I, Cabero M, Teijeira L, Arrazubi V, Torrego N, Campillo-Calatayud A, Elejalde I, Kochan G, Escors D: Predictive biomarkers for checkpoint inhibitor immune-related adverse events. Cancers (Basel) 15(5): 1629, 2023. DOI: 10.3390/cancers15051629

15 Diehl A, Yarchoan M, Hopkins A, Jaffee E, Grossman SA: Relationships between lymphocyte counts and treatment-related toxicities and clinical responses in patients with solid tumors treated with PD-1 checkpoint inhibitors. Oncotarget 8(69): 114268-114280, 2017. DOI: 10.18632/oncotarget.23217

16 Nakamura Y, Tanaka R, Maruyama H, Ishitsuka Y, Okiyama N, Watanabe R, Fujimoto M, Fujisawa Y: Correlation between blood cell count and outcome of melanoma patients treated with anti-PD-1 antibodies. Jpn J Clin Oncol 49(5): 431-437, 2019. DOI: 10.1093/jjco/hyy201

17 Ma Y, Ma X, Wang J, Wu S, Wang J, Cao B: Absolute eosinophil count may be an optimal peripheral blood marker to identify the risk of immune-related adverse events in advanced malignant tumors treated with PD-1/PD-L1 inhibitors: a retrospective analysis. World J Surg Oncol 20(1): 242, 2022. DOI: 10.1186/s12957-022-02695-y

18 Ruste V, Goldschmidt V, Laparra A, Messayke S, Danlos FX, Romano-Martin P, Champiat S, Voisin AL, Baldini C, Massard C, Laghouati S, Marabelle A, Lambotte O, Michot JM: The

determinants of very severe immune-related adverse events associated with immune checkpoint inhibitors: A prospective study of the French REISAMIC registry. Eur J Cancer 158: 217-224, 2021. DOI: 10.1016/j.ejca.2021.08.048

19 Pavan A, Calvetti L, Dal Maso A, Attili I, Del Bianco P, Pasello G, Guarneri V, Aprile G, Conte P, Bonanno L: Peripheral blood markers identify risk of immune-related toxicity in advanced non-small cell lung cancer treated with immune-checkpoint inhibitors. Oncologist 24(8): 1128-1136, 2019. DOI: 10.1634/theoncologist.2018-0563

20 Eun Y, Kim IY, Sun JM, Lee J, Cha HS, Koh EM, Kim H, Lee J: Risk factors for immune-related adverse events associated with anti-PD-1 pembrolizumab. Sci Rep 9(1): 14039, 2019. DOI: 10.1038/s41598-019-50574-6

21 Liu W, Liu Y, Ma F, Sun B, Wang Y, Luo J, Liu M, Luo Z: Peripheral blood markers associated with immune-related adverse effects in patients who had advanced non-small cell lung cancer treated with PD-1 inhibitors. Cancer Manag Res 13: 765-771, 2021. DOI: 10.2147/CMAR.S293200

22 Bai R, Chen N, Chen X, Li L, Song W, Li W, Zhao Y, Zhang Y, Han F, Lyu Z, Cui J: Analysis of characteristics and predictive factors of immune checkpoint inhibitor-related adverse events. Cancer Biol Med 18(4): 1118-1133, 2021. DOI: 10.20892/j.issn.2095-3941.2021.0052

23 Fujimoto A, Toyokawa G, Koutake Y, Kimura S, Kawamata Y, Fukuishi K, Yamazaki K, Takeo S: Association between pretreatment neutrophil-to-lymphocyte ratio and immune-related adverse events due to immune checkpoint inhibitors in patients with non-small cell lung cancer. Thorac Cancer 12(15): 2198-2204, 2021. DOI: 10.1111/1759-7714.14063

24 Michailidou D, Khaki AR, Morelli MP, Diamantopoulos L, Singh N, Grivas P: Association of blood biomarkers and autoimmunity with immune related adverse events in patients with cancer treated with immune checkpoint inhibitors. Sci Rep 11(1): 9029, 2021. DOI: 10.1038/s41598-021-88307-3

25 Suazo-Zepeda E, Bokern M, Vinke PC, Hiltermann TJN, de Bock GH, Sidorenkov G: Risk factors for adverse events induced by immune checkpoint inhibitors in patients with non-small-cell lung cancer: a systematic review and meta-analysis. Cancer Immunol Immunother 70(11): 3069-3080, 2021. DOI: 10.1007/s00262-021-02996-3

26 Egami S, Kawazoe H, Hashimoto H, Uozumi R, Arami T, Sakiyama N, Ohe Y, Nakada H, Aomori T, Ikemura S, Fukunaga K, Yamaguchi M, Nakamura T: Peripheral blood biomarkers predict immune-related adverse events in non-small cell lung cancer patients treated with pembrolizumab: a multicenter retrospective study. J Cancer 12(7): 2105-2112, 2021. DOI: 10.7150/jca.53242

27 Xu H, Feng H, Zhang W, Wei F, Zhou L, Liu L, Zhao Y, Lv Y, Shi X, Zhang J, Ren X: Prediction of immune-related adverse events in non-small cell lung cancer patients treated with immune checkpoint inhibitors based on clinical and hematological markers: Real-world evidence. Exp Cell Res 416(1): 113157, 2022. DOI: 10.1016/j.yexcr.2022.113157

28 Lee PY, Oen KQX, Lim GRS, Hartono JL, Muthiah M, Huang DQ, Teo FSW, Li AY, Mak A, Chandran NS, Tan CL, Yang P, Tai ES, Ng KWP, Vijayan J, Chan YC, Tan LL, Lee MB, Chua HR, Hong WZ, Yap ES, Lim DK, Yuen YS, Chan YH, Aminkeng F, Wong ASC, Huang Y, Tay SH: Neutrophil-to-lymphocyte ratio predicts development of immune-related adverse events and outcomes from immune checkpoint blockade: a case-control study. Cancers (Basel) 13(6): 1308, 2021. DOI: 10.3390/cancers13061308

29 Chu X, Zhao J, Zhou J, Zhou F, Jiang T, Jiang S, Sun X, You X, Wu F, Ren S, Zhou C, Su C: Association of baseline peripheral-blood eosinophil count with immune checkpoint inhibitor-related pneumonitis and clinical outcomes in patients with non-small cell lung cancer receiving immune checkpoint inhibitors. Lung Cancer 150: 76-82, 2020. DOI: 10.1016/j.lungcan.2020.08.015

30 Drobni ZD, Zafar A, Zubiri L, Zlotoff DA, Alvi RM, Lee C, Hartmann S, Gilman HK, Villani AC, Nohria A, Groarke JD, Sullivan RJ, Reynolds KL, Zhang L, Neilan TG: Decreased absolute lymphocyte count and increased neutrophil/lymphocyte ratio with immune checkpoint inhibitor-associated myocarditis. J Am Heart Assoc 9(23): e018306, 2020. DOI: 10.1161/JAHA.120.018306

31 Takada S, Murooka H, Tahatsu K, Yanase M, Umehara K, Hashishita H, Toru H, Satoru M, Sagawa T, Fujikawa K, Sato H, Mino K: Identifying early predictive markers for immune-related adverse events in nivolumab-treated patients with renal cell carcinoma and gastric cancer. Asian Pac J Cancer Prev 23(2): 695-701, 2022. DOI: 10.31557/APJCP.2022.23.2.695

32 Fujisawa Y, Yoshino K, Otsuka A, Funakoshi T, Fujimura T, Yamamoto Y, Hata H, Gosho M, Tanaka R, Yamaguchi K, Nonomura Y, Hirai I, Furudate S, Okuhira H, Imafuku K, Aoki M, Matsushita S: Fluctuations in routine blood count might signal severe immune-related adverse events in melanoma patients treated with nivolumab. J Dermatol Sci 88(2): 225-231, 2017. DOI: 10.1016/j.jdermsci.2017.07.007

33 Egami S, Kawazoe H, Hashimoto H, Uozumi R, Arami T, Sakiyama N, Ohe Y, Nakada H, Aomori T, Ikemura S, Fukunaga K, Yamaguchi M, Nakamura T: Absolute lymphocyte count predicts immune-related adverse events in patients with non-small-cell lung cancer treated with nivolumab monotherapy: a multicenter retrospective study. Front Oncol 11: 618570, 2021. DOI: 10.3389/fonc.2021.618570

34 Zhang Z, Xie T, Qi C, Zhang X, Shen L, Peng Z: Peripheral blood biomarkers predictive of efficacy outcome and immune-related adverse events in advanced gastrointestinal cancers treated with checkpoint inhibitors. Cancers (Basel) 14(15): 3736, 2022. DOI: 10.3390/cancers14153736

35 Valero C, Zanoni DK, McGill MR, Ganly I, Morris LGT, Quer M, Shah JP, Wong RJ, León X, Patel SG: Pretreatment peripheral blood leukocytes are independent predictors of survival in oral cavity cancer. Cancer 126(5): 994-1003, 2020. DOI: 10.1002/cncr.32591

36 Cedrés S, Torrejon D, Martínez A, Martinez P, Navarro A, Zamora E, Mulet-Margalef N, Felip E: Neutrophil to lymphocyte ratio (NLR) as an indicator of poor prognosis in stage IV non-small cell lung cancer. Clin Transl Oncol 14(11): 864-869, 2012. DOI: 10.1007/s12094-012-0872-5

37 Azab B, Bhatt VR, Phookan J, Murukutla S, Kohn N, Terjanian T, Widmann WD: Usefulness of the neutrophil-to-lymphocyte ratio in predicting short- and long-term mortality in breast cancer patients. Ann Surg Oncol 19(1): 217-224, 2012. DOI: 10.1245/s10434-011-1814-0

38 Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, Clarke SJ: The systemic inflammation-based neutrophil-lymphocyte ratio: Experience in patients with cancer. Crit Rev Oncol Hematol 88(1): 218-230, 2013. DOI: 10.1016/j.critrevonc.2013.03.010

39 Stotz M, Gerger A, Eisner F, Szkandera J, Loibner H, Ress AL, Kornprat P, AlZoughbi W, Seggewies FS, Lackner C, Stojakovic T, Samonigg H, Hoefler G, Pichler M: Increased neutrophil-lymphocyte ratio is a poor prognostic factor in patients with primary operable and inoperable pancreatic cancer. Br J Cancer 109(2): 416-421, 2013. DOI: 10.1038/bjc.2013.332

40 Walsh SR, Cook EJ, Goulder F, Justin TA, Keeling NJ: Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. J Surg Oncol 91(3): 181-184, 2005. DOI: 10.1002/jso.20329

41 Persano M, Rimini M, Tada T, Suda G, Shimose S, Kudo M, Cheon J, Finkelmeier F, Lim HY, Presa J, Masi G, Yoo C, Lonardi S, Pressiani T, Piscaglia F, Kumada T, Rimassa L, Scartozzi M, Cascinu S, Casadei-Gardini A, HCC COLLABORATIVE GROUP: Identification of atezolizumab plus bevacizumab prognostic index *via* recursive partitioning analysis in HCC: The ABE index. Anticancer Res 43(4): 1599-1610, 2023. DOI: 10.21873/anticanres.16310

42 Eso Y, Takeda H, Taura K, Takai A, Takahashi K, Seno H: Pretreatment neutrophil-to-lymphocyte ratio as a predictive marker of response to atezolizumab plus bevacizumab for hepatocellular carcinoma. Curr Oncol 28(5): 4157-4166, 2021. DOI: 10.3390/curroncol28050352

43 Tada T, Kumada T, Hiraoka A, Hirooka M, Kariyama K, Tani J, Atsukawa M, Takaguchi K, Itobayashi E, Fukunishi S, Tsuji K, Ishikawa T, Tajiri K, Ochi H, Yasuda S, Toyoda H, Ogawa C, Nishimura T, Hatanaka T, Kakizaki S, Shimada N, Kawata K, Tanaka T, Ohama H, Nouso K, Morishita A, Tsutsui A, Nagano T, Itokawa N, Okubo T, Arai T, Imai M, Naganuma A, Koizumi Y, Nakamura S, Joko K, Iijima H, Hiasa Y, Real-life Practice Experts for HCC (RELPEC) Study Group and the Hepatocellular Carcinoma Experts from 48 clinics in Japan (HCC 48) Group: Neutrophil-lymphocyte ratio predicts early outcomes in patients with unresectable hepatocellular carcinoma treated with atezolizumab plus bevacizumab: a multicenter analysis. Eur J Gastroenterol Hepatol 34: 698-706, 2022. DOI: 10.1097/MEG.0000000000002356

44 Takeda S, Namisaki T, Tsuji Y, Fujimoto Y, Murata K, Enomoto M, Fujinaga Y, Nishimura N, Kitagawa K, Takaya H, Kaji K, Inoue T, Kawaratani H, Akahane T, Mitoro A, Yoshiji H: Initial experience with atezolizumab plus bevacizumab for unresectable hepatocellular carcinoma: a real-world retrospective study. Anticancer Res 42(11): 5465-5473, 2022. DOI: 10.21873/anticanres.16051

45 Ng KYY, Tan SH, Tan JJE, Tay DSH, Lee AWX, Ang AJS, Wong LWJ, Choo SP, Tai DW, Lee JJX: Impact of immune-related adverse events on efficacy of immune checkpoint inhibitors in patients with advanced hepatocellular carcinoma. Liver Cancer 11(1): 9-21, 2021. DOI: 10.1159/000518619

46 Fukushima T, Morimoto M, Kobayashi S, Ueno M, Uojima H, Hidaka H, Kusano C, Chuma M, Numata K, Tsuruya K, Arase Y, Kagawa T, Hattori N, Ikeda H, Watanabe T, Tanaka K, Maeda S: Association between immune-related adverse events and survival in patients with hepatocellular carcinoma treated with atezolizumab plus bevacizumab. Oncologist 28(7): e526-e533, 2023. DOI: 10.1093/oncolo/oyad090

47 Hatanaka T, Kakizaki S, Hiraoka A, Tada T, Hirooka M, Kariyama K, Tani J, Atsukawa M, Takaguchi K, Itobayashi E, Fukunishi S, Tsuji K, Ishikawa T, Tajiri K, Ochi H, Yasuda S, Toyoda H, Ogawa C, Nishimura T, Shimada N, Kawata K, Kosaka H, Tanaka T, Ohama H, Nouso K, Morishita A, Tsutsui A, Nagano T, Itokawa N, Okubo T, Arai T, Imai M, Naganuma A, Koizumi Y, Nakamura S, Joko K, Kaibori M, Iijima H, Hiasa Y, Kumada T, Real-life Practice Experts for HCC (RELPEC) Study Group, and HCC 48 Group (hepatocellular carcinoma experts from 48 clinics in Japan): Comparative efficacy and safety of atezolizumab and bevacizumab between hepatocellular carcinoma patients with viral and non-viral infection: A Japanese multicenter observational study. Cancer Med 12(5): 5293-5303, 2023. DOI: 10.1002/cam4.5337

48 Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS Jr, Bzowej NH, Wong JB: Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 67(4): 1560-1599, 2018. DOI: 10.1002/hep.29800

49 Ferreira J, Oliveira M, Bicho M, Serejo F: Role of inflammatory/immune response and cytokine polymorphisms in the severity of chronic hepatitis C (CHC) before and after direct acting antiviral (DAAs) treatment. Int J Mol Sci 24(2): 1380, 2023. DOI: 10.3390/ijms24021380

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