Are Markers of Systemic Inflammatory Response Useful in the Management of Patients With Neuroendocrine Neoplasms?

Elisa Giannetta1*, Anna La Salvia2, Laura Rizza3, Giovanna Muscogiuri4, Severo Campione5, Carlotta Pozza1, Annamaria Anita Livia Colao6 and Antongiulio Faggiano7 on behalf of NIKE

1 Department of Experimental Medicine, “Sapienza” University of Rome, Rome, Italy, 2 Department of Oncology, University Hospital 12 de Octubre, Madrid, Spain, 3 Endocrinology Unit, Department of Oncology and Medical Specialties, AO San Camillo-Forlanini, Rome, Italy, 4 Endocrinology Unit Department of Clinical Medicine and Surgery, University Federico II School of Medicine, Naples, Italy, 5 A. Cardarelli Hospital, Naples Department of Advanced Diagnostic-Therapeutic Technologies and Health Services Section of Anatomic Pathology, Naples, Italy, 6 Department of Clinical Medicine and Surgery, University “Federico II”, Naples, Italy, 7 Department of Clinical and Molecular Medicine, Endocrine-Metabolic Unit, Sant’Andrea University Hospital “Sapienza” University of Rome, Rome, Italy

Given the increasing incidence of neuroendocrine neoplasms (NENs) over the past few decades, a more comprehensive knowledge of their pathophysiological bases and the identification of innovative NEN biomarkers represents an urgent unmet need. There is still little advance in the early diagnosis and management of these tumors, due to the lack of sensible and specific markers with prognostic value and ability to early detect the response to treatment. Chronic systemic inflammation is a predisposing factor for multiple cancer hallmarks, as cancer proliferation, progression and immune-evading. Therefore, the relevance of inflammatory biomarkers has been identified as critical in several types of tumours, including NENs. A bidirectional relationship between chronic inflammation and development of NENs has been reported. Neuroendocrine cells can be over-stimulated by chronic inflammation, leading to hyperplasia and neoplastic transformation. As the modulation of inflammatory response represents a therapeutic target, inflammatory markers could represent a promising new key tool to be applied in the diagnosis, the prediction of response to treatment and also as prognostic biomarkers in NENs field. The present review provides an overview of the pre-clinical and clinical data relating the potentially usefulness of circulating inflammatory markers: neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), cytokines and tissue inflammatory markers (PD-1/PD-L1), in the management of NENs. (1) NLR and PLR have both demonstrated to be promising and simple to acquire biomarkers in patients with advanced cancer, including NEN. To date, in the context of NENs, the prognostic role of NLR and PLR has been confirmed in 15 and 4 studies, respectively. However, the threshold value, both for NLR and PLR, still remains not defined. (2) Cytokines seem to play a central role in NENs tumorigenesis. In particular, IL-8 levels seems to be a good predictive marker of response to anti-angiogenic treatments. (3) PD-1 and PD-L1...
INTRODUCTION

The physiopathological association between chronic inflammation and cancer has been established for a long time (1–3). Although chronic inflammatory milieu could contribute to the development of cancer, several studies reported that tumor itself could begin and keep an inflammatory process up. A change in a set of cytokines and chemokines has been reported in studies regarding stomach (4), liver (5, 6), lung (7), esophagus (8), breast (9), and prostate cancer (10). These findings could be of interest to identify not only potential pathogenetic mechanisms but also novel diagnostic/prognostic markers (11). In this view, recent studies analyzed the immunophenotypes of cancer cells and cancer stromal cells in terms of usefulness as prognostic factors, showing the prognostic values of podoplanin-positive cancer-associated fibroblasts (CAFs) for patients with high-grade neuroendocrine carcinomas (HG-NEC) of the lung (12).

An important hallmark of cancer is that it can escape immune attack; therefore, chronic cancer-related inflammation could be considered as an attempt of immunosuppression mechanisms mediated primarily by immature myeloid-derived suppressor cells to block the development of cancer (13, 14). The fascinating link between inflammation and the field of neuroendocrinology has also been evaluated (15, 16). A bidirectional action between neuroendocrine stimuli and macrophage function in the development of innate and adaptive immune responses was described (17), suggesting a potential involvement of inflammation in the development of neuroendocrine neoplasms (NENs).

Neuroendocrine cells can be over-stimulated by chronic inflammation, which leads to hyperplasia and neoplastic transformation (18).

Research efforts have shown that NENs of gastroenteropancreatic tract (GEP-NENs) occur more frequently in the settings of chronic inflammation. Indeed, it was shown that enteroendocrine cells can be hyperstimulated by chronic inflammation, which leads to their hyperplasia and neoplastic transformation (19–21).

Despite the progress in the understanding of NEN molecular biology, we are still far from the identification of markers able to detect the tumor at an early stage as well as to predict disease relapse after treatments.

As the modulation of inflammatory response represents a therapeutic target, changes of inflammatory markers may potentially represent in the future new biomarkers, which beyond the RECIST criteria, could eventually be helpful in the follow up of patient with NENs treated with targeted therapies.

This review investigated a panel of inflammatory response markers apparently heterogeneous but sharing the feature to be readily available and inexpensive diagnostic and prognostic factors in NENs.

PROGNOSTIC VALUE OF NEUTROPHIL-TO-LYMPHOCYTE RATIO AND PLATELET-TO-LYMPHOCYTE RATIO FOR PATIENTS WITH NEN

The recent advent of detecting systemic inflammation levels through non-invasive blood tests, has opened the possibility of studying inflammatory processes at baseline and monitoring the course of cancer disease, in order to stratify patients according to their prognosis and to achieve a personalized approach (22). In this context, two ratios, neutrophil-lymphocyte ratio (NLR, calculated as the neutrophil count divided by the lymphocyte count) and platelet-lymphocyte ratio (PLR, obtained by dividing the platelet count by the absolute number of lymphocytes), have demonstrated to be powerful biomarkers for patients with cancer (23, 24). Notably, both NLR and PLR, are non-invasive, rapid, simple to acquire and inexpensive markers, thus, they could have a potential for widespread clinical use.

High NLR has been associated with poor clinical outcome in several tumor types (25). The underlying mechanism has not completely been elucidated, so far. Preclinical studies have shown that neutrophilia, which is a direct expression of systemic inflammation, represses the cytolytic activity of immune cells, such as lymphocytes, activated T cells, and natural killer cells (26). Additionally, tumor-associated neutrophils (TANs) have been demonstrated to promote tumor progression acting as pro-angiogenic agents (27), by a high expression of different pro-angiogenic factors as vascular endothelial growth factor (VEGF), Interleukin 1 beta (IL-1β) and Integrin Subunit Beta 1 (ITGB1) (28). Several studies have also reported that TANs are associated with an elevated expression of matrix metallopeptidase-9 (MMP-9), favoring angiogenesis through the MMP-9-VEGF axis (28).

PLR has arisen as a useful marker of systemic inflammation, metabolic syndrome and prothrombotic state and it is regarded as a promising biomarker in cancer patients (24, 29). Alterations in PLR have also been associated with other markers of systemic inflammation, particularly with NLR. Even in this case, as for NLR, the molecular mechanism has not been fully understood yet. Platelets represent an essential storage for secreted growth factors (as VEGF or platelet-derived growth factor, PDGF).
In that way, platelets play a key role in regulating tumor angiogenesis, cell proliferation, migration, and metastasis (30, 31).

Therefore, despite the encouraging data about the clinical relevance and prognostic implication of NLR and PLR as biomarkers in cancer patients, some limitations still exist. For instance, a unique cut-off value of these two inflammatory ratios has not been established. Another open issue is to determine the best timing for dosing NLR and PLR, given the dynamic nature of this measures that change over times and that could be altered in relation to the administration of systemic treatments or because of other clinical conditions (as sepsis and septic shock) (32).

Clinical Evidence in NENs

To date, several studies have been published about the role of the two ratios, NLR and PLR, in NENs. The available data are summarized in Table 1.

In 2016 the Izmir Oncology Group Study retrospectively investigated the prognostic role of baseline NLR and PLR in 132 GEP-NENs patients. The included patients were equally distributed according to grading (31.1% G1, 33.3% G2, 35.6% G3). Embryonic origin was foregut in 87 cases, midgut in 20 cases and hindgut in 25. Primary site was pancreas in 50 cases and gastro-enteric tract in 82. 62 were metastatic patients. NLR and PLR were significantly higher in high grade NENs (0.0001), in metastatic patients (0.0001) and in those of foregut origin (0.0001). Patients with pancreatic NENs had higher NLR and PLR compared to those with gastrointestinal NENs (0.0001). Finally, higher NLR and PLR were negatively associated to progression-free survival (PFS) (0.0001), while no overall survival (OS) data were provided (13).

Another study, by Cao et al., evaluated the prognostic role of preoperative NLR in 147 gastric NENs (g-NENs) patients that underwent to radical surgery. Of them, 27 (18.4%) patients were gastric neuroendocrine tumors (g-NETs), 48 (32.7%) with gastric neuroendocrine carcinoma (g-NEC), and 72 (48.9%) with gastric mixed adenoneuroendocrine carcinoma (g-MANE C). Among these patients, 97 (66.0%) received adjuvant chemotherapy. Moreover, 147 healthy controls were enrolled. Significantly higher value of NLR was detected in patients with g-NENs compared to controls (P < 0.001). Furthermore, the NLR was an independent prognostic factor of relapse free survival (RFS) and OS (p<0.05 for both outcome measures), and, along with Ki67, positively correlated with liver metastases and negatively correlated with recurrence time (16).

One year later, a retrospective study aimed to evaluate the role of preoperative NLR as prognostic marker, was performed by Arima et al. (15). All the 58 pancreatic NENs patients included in the analysis, underwent curative pancreatic resection. Among these 58 patients, 46 were well differentiated G1 pancreatic neuroendocrine tumors (pNETs) and 31 were non-functioning tumors. The median NLR of all pNENs 58 patients was 2.18. A high preoperative NLR was significantly associated with higher tumor size (p=0.0015) and grade 3 (p<0.0001). In this analysis, the authors were able to identify a cut off value of NLR ≥2.4, that resulted associated to a worst OS (P = 0.0481) and RFS (P < 0.0001) and to an increased risk of postoperative recurrence (p= 0.0035).

In the same year, other three similar retrospective analysis were performed. All these three studies included G1, G2 and G3 pNENs. The first, included a population of 95 operated pancreatic NENs (33). Among these patients, 52 (54.7%) were G1 NET, 32 (33.7%) G2 NET, and 11 (11.6%) G3 NEC. A significant association was found between high NLR and advanced T stage, nodal metastasis, and advanced grade (p< 0.05 for all variables). High NLR value was confirmed as an independent prognostic factor for lymph-node metastasis by multivariate logistic regression (Hazard ratio (HR) 6.74; p=0.02)). NLR higher than 1.4 correlated with decreased RFS (p < 0.05). A second study, by Zhou B et al., evaluated both NLR and PLR in 172 patients with pNENs (34). 73 (42.4%) were G1 pNETs, 76 (44.2%) G2, and 23 (13.4%) G3 pancreatic NEC. 150 cases (87.2%) had stage I-II disease. 166 patients (96.5%), underwent R0 resection and 6 cases received palliative surgery (3.5%). In the study were enrolled also 172 healthy volunteers. A cut-off for NLR was identified as 2.31, for PLR was 151.4. NLR and PLR were significantly higher in the patients than in controls (all p<0.001). At univariate analysis an increased NLR and PLR correlated with advanced stage, high grade, and R1 resection (all p<0.05). High NLR or PLR had shorter OS (HR=4.907, p<0.001 and HR=3.307, p=0.003, respectively) and disease-free survival, DFS (HR=4.143, p<0.001 and HR=2.617, p<0.001, respectively) than patients with a low NLR or PLR. However, at multivariate analysis, only NRL remained significant as independent prognostic factor in terms of OS (HR=4.47, p=0.006) and DFS (HR=2.531, p=0.015). The third study, by Zhou et al., analyzed preoperative NLR and PLR in a population of 101 surgically removed pNENs (35). In this study, cutoff values were 1.80 for NLR and 168.25 for PLR. NLR and PLR were significantly higher in those patients with lymph-nodes metastases (p<0.05). At multivariable analysis, NLR (p=0.017) correlated with lymph-nodes metastases. High NLR or PLR had shorter DFS (p=0.007 and p<0.001, respectively).

One year later, in 2018, a prospective study evaluating the role of NLR (calculated at baseline and preoperatively) and PLR (calculated at the time of enrollment for all patients, as well as preoperatively for patients who underwent resection with curative intent) in 97 pNENs, was published (37). The authors found that NLR higher than a cut-off values of 2.3 was a negative prognostic factor in terms PFS (HR 2.53, p = 0.038) and at multivariant analysis PLR > 160.9 resulted independently associated with reduced DFS (p= 0.023).

Another interesting retrospective study evaluated the role of NLR in a population of 26 completely resected large cells neuroendocrine carcinomas (LCNEC) (36). Notably, at multivariate analysis, a preoperative NLR value > 1.7 was confirmed as an independent prognostic factor for OS (HR 8.559, p = 0.011).

McDermott and colleagues, instead, investigated the prognostic value of NLR in 262 stage IV patients with liver metastases from different primary origins (GEP and pulmonary primary tumor), who were treated with transarterial chemoembolization (TACE) (38). As a result, pre-TACE NLR > 4 was associated with shorter OS.
| Author, year | Mean age | Primary site | Grade | TNM stage | Metastasis | NLR cut-off | PLR cut-off |
|-------------|----------|--------------|-------|-----------|------------|-------------|-------------|
| Salman T. et al. (13) | 56.7 | GEP-NENs | 1-2-3 | 1-2-3-4 | Metastatic & Non-metastatic | 2.17 | 181.5 |
| Cao L-L. et al. (16) | 58 | Gastric NENs | 1-2-3 | 1-2-3-4 | Metastatic & Non-metastatic | 2.20 | / |
| Arima K. et al. (15) | 58 | Pancreatic-NENs | 1-2-3 | / | Metastatic & Non-metastatic | 2.40 | / |
| Tong Z. et al. (33) | 54.4 | Pancreatic-NENs | 1-2-3 | 1-2-3-4 | Metastatic & Non-metastatic | 1.40 | / |
| Zhou B. et al. (34) | 52.9 | Pancreatic-NENs | 1-2-3 | 1-2-3-4 | Metastatic & Non-metastatic | 2.31 | / |
| Zhou B. et al. (35) | 53 | Non-functioning Pancreatic-NENs | 1-2-3 | 1-2-3-4 | Metastatic & Non-metastatic | 1.80 | 151.4 |
| Okui M. et al. (36) | 68.8 | LCNEC | 3 | 1-2-3 | Non metastatic | 1.70 | 168.25 |
| Gaitanidis A. et al. (37) | 52 | Pancreatic-NENs | 1-2-3 | / | Metastatic & Non-metastatic | 2.3 | / |
| McDermott SM. et al. (38) | 57 | GEP, colorectal and lung NENs | 1-2-3 | 4 | Metastatic | 4 | / |
| Zou J. et al. (39) | 65 | GEP, colorectal and other NENs | 1-2-3 | 4 | Metastatic & Non-metastatic | 2.8 | / |
| Panni RZ. et al. (40) | 57.5 | Pancreatic-NENs | 1-2-3 | 1-2-3 | Non-metastatic | 3.7 | / |
| Harimoto N. et al. (41) | 61 | Pancreatic-NENs | 1-2-3 | 1-2-3 | Non-metastatic | 3.4 | 160.9 |
| Pozza A. et al. (42) | 70, 66 | Foregut, Midgut and hindgut NEN | 1-2-3 | 1-2-3-4 | Metastatic & Non-metastatic | 2.6 | / |
| Zhou B. et al. (43) | 60 | Pancreatic-NENs | 1-2-3 | 1-2-3-4 | Metastatic & Non-metastatic | 3.1 | / |
| Zhou W. et al. (44) | 53 | Pancreatic-NENs | 1-2-3 | 1-2-3-4 | Metastatic & Non-metastatic | 1.9 | / |

GEP, gastro-entero-pancreatic; HR, hazard ratio; NEC, neuroendocrine carcinomas; NENs, neuroendocrine neoplasms; PFS, progression free survival; RFS, recurrence free survival; OS, overall survival.
(p=0.005). Additionally, pre-TACE NLR and 6-months post-TACE NLR resulted independently associated with OS on multivariable analysis (HR 1.4 p=0.030 and HR 1.7 0.007, respectively).

Another study focused on locally advanced and metastatic patients was performed in 2019 by the group of Zou and colleagues (39). In this case, were included 135 G1, G2 and G3 NENs of different primary origin. At univariate analysis, NLR > 2.8 correlated with OS (p=0.003), but the statistical significance was not confirmed at multivariant analysis.

Additionally, a year later in 2019, four retrospective analyses, which investigated the prognostic role of inflammatory markers in surgically removed pNENs patients were published. The first of them, included 620 non metastatic G1, 2 and 3 patients (40). With a cut-off of NLR of 3.7, the authors demonstrated a significative impact on RFS (HR 1.79, p=0.01) and OS (HR 2.04, p=0.01). The second study, by Harimoto N and colleagues, included 55 pNEN patients (41) and showed a negative prognostic role (in terms of RFS) for NLR>3.4, on univariate analysis (HR 12.62, p<0.01) and multivariate analysis (HR 31.75, p=0.03). The third analysis was conducted on 64 operated pNENs (43). In this study, high NLR correlated with poor OS and DFS compared to patients with a low NLR score (p < 0.001). In the multivariate analysis, high NLR resulted an independent prognostic factor in terms of OS and DFS for pNENs of the head (p=0.002 and p<0.001, respectively). The fourth study, by Zhou W et al., included 174 pNENs (44). Even in this case, the prognostic role for NLR, with a cut-off of 1.9, was confirmed at univariate analysis, both in RFS (p=0.046) and in OS (p=0.032). However, multivariate analysis did not confirm that the NLR had an independent prognostic impact”.

Finally, a study on 48 G1, G2 and G3 NENs of different primary origins, but all surgically removed, was carried on by an Italian group (42). By a threshold value for NLR of 2.6, at the multivariant analysis high NLR was confirmed to have a significant impact on OS (HR 4.71, p = 0.02).

Future Directions
Proinflammatory signals promote tumorigenesis and neoplastic progression, but their origins and downstream effects remain unclear. Given the pooled data of these studies about NLR and PLR, that confirm their role, these two inflammatory biomarkers could potentially represent innovative prognostic factors for NENs. In fact, both NLR and PLR are rapid, easy to measure, and cheap to obtain from routinary blood tests. In the analyzed studies both of them have been demonstrated to correlate with RFS and OS. Additionally, their combination with other markers such as proliferation index (ki67) and for example lymph node ratio, in order to obtain nomograms, has demonstrated to have a higher power to predict clinical outcomes of NEN patients (45). Polymorphonuclear neutrophils (PMN) also represent critical innate immune effector cells that either protect the host or exacerbate organ dysfunction by migrating to injured or inflamed tissues. Pathways including neuroendocrine and innate and acquired immune systems regulates PMN mobilization. In this view there is still no evidence of an accumulation of PMN in the NENs, but this aspect deserves to be examined (46).

However, there are many limitations of these data and some open questions. First of all, almost all the studies considered are retrospective and the sample size is quite often little. Furthermore, both the cut-off value used, and the population included is highly heterogeneous. Unfortunately, considering these issues a strong recommendation to the direct application in the clinical practice of NLR or PLR, couldn’t be given. However, the data presented are promising and should be confirmed in further prospective study, given the striking need to find new biomarkers in the field of NENs in order to better stratify patients by prognosis and to improve the personalization of therapeutic strategy.

CIRCULATING CYTOKINES AS POSSIBLE BIOMARKERS OF THERAPEUTIC RESPONSE IN PATIENTS WITH NEN

The key molecular links between inflammation and cancer involve the canonical nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation and Signal transducer and activator of transcription 3 (STAT3) pathways (47). NF-κB and STAT3 signaling pathways control genes necessary for angiogenesis (mainly VEGF) and influence the ability of tumor cells to invade and metastasize (48, 49). As a rule, most proinflammatory cytokines including tumor necrosis factor α (TNF-α), interleukin 6 (IL-6) and interleukin 17 (IL-17), produced by either the host immune system or the tumor cells themselves, promote tumor progression. In turn, pro-apoptotic TNF-related apoptosis-inducing ligand (TRAIL) and anti-inflammatory cytokines such as Interleukin 10 (IL-10) and transforming growth factor beta (TGF-β) usually lead to tumor suppression (50).

Clinical Evidences in NEN
The role of cytokines (such as IL-1) in NENs differentiation has been demonstrated (51). Furthermore, Interleukin 2 (IL-2) has an established role in the regulation of the neuroendocrine system and in gastrointestinal hormone synthesis and secretion (52). Although normal pancreatic cells do not express Interleukin 8 (IL-8), pNENs show increased expression of IL-8 and its receptors, especially C-X-C Motif Chemokine Receptor 2 (CXCR2) (53, 54). In low-grade pNENs, normal circulating Placental Growth Factor (PIGF) values are associated with better survival, while in low-grade small intestinal NENs (SI-NENs) is an independent prognostic factor for shorter time-to-progression (55). The overexpression of VEGF promotes the growth of human NENs in part through up-regulation of angiogenesis (56). Low-grade NENs can synthesize, store and secrete VEGF, while, in HG-NENs this process is inconstant and heterogeneous. This feature is part of the so-called “neuroendocrine paradox”: in pNENs the density of the vascular network reflects the rate of differentiation rather than of aggressiveness: most is the vascularization, less the aggressiveness, and more differentiated pNEN are the less angiogenic. In this view, a recent study analyzing 60 resected HG-NEC of the lung (37 LCNECs and 23 Small Cell Lung Carcinomas -SCLCs), revealed the presence of
stromal cells within vascular invasion was not significant predictor for recurrence. This suggests that the roles of intravascular stromal cells in HG-NEC metastasis are less, raise an “alarm” against overemphasis of stromal cell-targeting therapy (57).

Then, there is a strong rationale for supporting the use of angiogenesis inhibitor in well differentiated rather than poorly differentiated NENs. By contrast HG-pNENs are particularly active in terms of angiogenesis, meaning endothelial cell proliferation and abnormal vasculature (58).

In this view, cytokines panel represents an interesting tool in NENs, needing for framing. Cigrovski Berkovic et al. proposed a model of different cytokine genotypes and corresponding high serum values that regulate GEP-NEN etiopathogenesis (19).

Finally, Pavel et al. (59) showed that the circulating levels of VEGF and IL-8 are associated with tumor progression in patients with advanced NEC and might qualify as markers of prognosis and therapy control. Angiogenin and basic fibroblast growth factor (bFGF) levels do not correlate with tumor growth and with patient survival.

The prognostic utility of systemic inflammatory markers in NENs' patients after therapy is still debated. The first-in-human trial of sunitinib (SUN) (60) included an analysis of plasma levels of VEGF and its soluble receptor, sVEGFR-2, of twenty-eight cancer patients (among them 4 patients were NENs), both pretreatment and after 28 days of treatment. VEGF concentrations increased slightly during the first month of SUN, while the plasma mean sVEGFR-2 decreased, demonstrating a targeted effect of the drug. Comparable findings were observed in another study on patients with metastatic NENs (61). After 28 days of SUN administration, VEGF levels increased more than 3-fold over baseline in about half of all patients, while sVEGFR-2 and sVEGFR-3 levels decreased by ≥ 30% in about 60% and 70% of all patients, respectively. Levels returned to baseline after two weeks of therapy interruption. Furthermore, IL8 values raised 2.2-fold average by the end of SUN cycle 1, and a larger increase was proportional to the tumor size reduction. This increase in IL-8 levels during SUN treatment can represent a mechanism of drug resistance, as also reported by Huang (62) in renal clear-cell carcinomas (RCC) cell lines. In addition, Zurita et al. (63) report that, at four weeks of the first cycle, SUN treatment is associated with significant increases from baseline in VEGF, IL-8, and stromal cell-derived factor-1 (SDF-1a) (also known as C-X-C motif chemokine 12, CXCL12), and with reduction in sVEGFR-2 and sVEGFR-3 with no difference between 66 pNENs and 39 carcinoid tumors. No significant associations have been found between soluble protein levels and clinical benefit response or PFS in pNENs, while high sVEGFR-3 and IL-8 levels correlated with shorter PFS and shorter OS in carcinoid tumors. Additionally, recent data come from the Spanish prospective SALSUN clinical trial enrolling well-differentiated pancreatic neuroendocrine tumors treated with somatostatin (PMID: 30651923). In this study, two SNPs in the VEGFR-3 gene, rs307826 and rs307821, predicted lower OS, with HR 3.67 and with HR 3.84, respectively. IL-6 was associated with increased mortality: HR 1.06, and osteopontin was associated with shorter PFS: HR 1.087, independently of Ki-67 value. Furthermore, levels of osteopontin remained higher at the end of the study in patients considered non-responders: 38.5 ng/mL vs. responders: 18.7 ng/mL, p-value=0.039. Dynamic upward variations were also observed with respect to IL-8 levels in sunitinib-refractory individuals: 28.5 pg/mL at baseline vs. 38.3 pg/mL at 3 months, p-value=0.024. In the RADIANT-3 phase III randomized clinical trial (64), baseline and post-treatment VEGF, PIGF, bFGF, sVEGFR-1, and sVEGFR-2 values were investigated in advanced pNENs’ patients treated with everolimus (EVE) 10 mg/die. In relation to the placebo, EVE treatment leads a significant and progressive reduction in sVEGFR-2 and an early but not significant decrease in PIGF. No significant differences in circulating concentrations of VEGF or sVEGFR-1 were observed. These data suggest a possible antiangiogenic effect of EVE as consequence of mTOR inhibition.

With regard to somatostatin analogs and interferon, in 36 patients with metastatic or unresectable carcinoid tumors (65), treatment with PEG interferon + depot Octreotide was associated with a significant increase in plasma Interleukin 18 (IL-18) and a significant reduction in plasma bFGF. No significant changes in the same plasma cytokines were associated with bevacizumab + depot octreotide therapy. Bevacizumab therapy resulted in objective responses, reduction of tumor blood flow, and longer PFS in patients with carcinoid than PEG interferon treatment. Finally, eight patients with NENs present lower VEGF plasma levels and reduced VEGF mRNA levels and microvessel density in liver metastasis biopsy material after IFN-α treatment (66). Table 2 summarized circulating cytokine trend in response to different treatment approaches.

Future Perspectives

Cytokines seem to play a central role in NEN tumorigenesis. The observation that the modulation of IL-1 was positively related to a decrease in Chromogranin A (CgA) and a parallel increase in Carcinoembryonic antigen (CEA) secretion, suggest the key role of cytokines in NEN progression (51).

Together, the main results of the studies with large sample size suggest that the VEGF-pathway proteins and IL-8 are possible markers of prognosis and/or SUN treatment benefit in patients with GEP-NENs. Particularly, the IL-8 increase can represent a potential predictor of SUN response (61–63). VEGF, sVEGFR-2 and -3 changes can be new SUN’s biological activity biomarkers in NENs, confirming that SUN’s activity is mediated by the VEGF signaling pathway (60, 61, 63). Routine use of these circulating cytokines, in NEN patients’ clinical practice for SUN, is hopeful. Owing to the limited number of patients, further studies are needed to confirm the SDF-1α role in resistance to antiangiogenic SUN therapy.

A cross-talk between pro-inflammatory and angiogenic chemokines is described (67, 68). Interleukin-8 is an inflammatory cytokine upregulated in both cancer and chronic inflammatory diseases. Moreover, IL-8 is a chemokine that increases endothelial permeability during early stages of angiogenesis. IL-8 expression was inducible by hypoxia due to VEGF inhibition. In this view targeting both VEGF and IL8 it may be possible to achieve greater therapeutic efficacy.

As regard EVE treatment, except sVEGFR-2 and PIGF significant reduction, there are no significant differences in
VEGF-pathway circulating proteins (64). These data suggest a possible antiangiogenic effect of EVE as a consequence of mTOR inhibition. Probably, other NENs biomarkers [such as Neuron-specific enolase (NSE) and CgA] have a better prognostic value than the inflammatory cytokines in terms of survival and/or response to EVE treatment.

Given the strong rationale for using anti-angiogenic therapy for several tumors, basic and clinical research has shown a growing interest in investigating new related pathways (69). Tie2-expressing monocytes/macrophages (TEMs), Tie2 and VEGFR2 are highly expressed on stromal cells of the tumor microenvironment, especially on endothelial cells. Certain cancers, such as melanomas and gliomas, have been shown to lead to increased circulating Tie2+ monocytes and their recruitment to distal metastatic sites or anti-VEGF-treated gliomas (70). Recently an \textit{in vitro} study proposed that modulation of Tie2+ proangiogenic macrophages through rebastinib, could possibly control tumor angiogenesis and lymphangiogenesis involved in cancer cell intravasation and metastasis in a model of pNENs (71). Our suggestion is that by identifying proinflammatory pathways in NENs we could extrapolate a set of prognostic markers useful in the management of NENs.

### PREDICTIVE AND PROGNOSTIC VALUE OF PD1 AND PD-L1 FOR PATIENTS WITH NEN

A key role in the immune-escape process is related to the interaction between programmed cell death protein 1 receptor

---

**TABLE 2 | Circulating cytokines trend according to different treatments.**

| Treatment | N° pts | Tumor types | Tumor site | Tumor stage | Author, Year |
|-----------|--------|-------------|------------|-------------|--------------|
| VEGF ↑ | SUN 4 | NEN digestive system | advanced (1/4 rectum) | Falvre S. (60) |
| VEGF ↓ | SUN 4 | NEN digestive system | advanced (1/4 rectum) | Falvre S. (60) |
| VEGF ↑ | SUN 109 | NEN pancreas | advanced | Bello CL. (61) |
| VEGF ↓ | SUN 109 | NEN pancreas | advanced | Bello CL. (61) |
| IL8 ↑ | SUN 109 | NEN pancreas | advanced | Zurita AJ. (63) |
| VEGF ↑ | SUN 65 | NEN pancreas | advanced | Zurita AJ. (63) |
| IL-8 ↑ | SUN 35 | carcinoma foregut, midgut, hindgut | advanced (unresectable or metastatic) | Zurita AJ. (63) |
| SDF-1a ↑ | SUN 11 | NEN pancreas | advanced (unresectable or metastatic) | Zurita AJ. (63) |
| IL8 ↑ | SUN 36 | carcinoma foregut, midgut, hindgut | advanced (unresectable or metastatic) | Zurita AJ. (63) |
| IL18 ↑ | SUN 10 | carcinoma foregut, midgut, hindgut | advanced (unresectable or metastatic) | Zurita AJ. (63) |
| IL18 ↑ | SUN 65 | NEN pancreas | advanced (unresectable or metastatic) | Zurita AJ. (63) |
| IL18 ↑ | SUN 37 | carcinoma foregut, midgut, hindgut | advanced (unresectable or metastatic) | Zurita AJ. (63) |
| IL18 ↑ | SUN 64 | NEN pancreas | advanced (unresectable or metastatic) | Zurita AJ. (63) |
| IL18 ↑ | SUN 34 | carcinoma foregut, midgut, hindgut | advanced (unresectable or metastatic) | Zurita AJ. (63) |
| PIGF ↑ | EVE 393 | NEN pancreas | low – intermediate; advanced (unresectable or metastatic) | Yao JC. (64) |
| PIGF ↓ | EVE 391 | NET pancreas | advanced (unresectable or metastatic) | Yao JC. (65) |
| sVEGFR1 = EVE 390 | NET pancreas | advanced (unresectable or metastatic) | Yao JC. (65) |
| sVEGFR2 = EVE 393 | NET pancreas | advanced (unresectable or metastatic) | Yao JC. (65) |
| VEGF = EVE 393 | NET pancreas | advanced (unresectable or metastatic) | Yao JC. (65) |
| VEGF = EVE 393 | NET pancreas | advanced (unresectable or metastatic) | Yao JC. (65) |
| VEGF = EVE 393 | NET pancreas | advanced (unresectable or metastatic) | Yao JC. (65) |
| IL18 ↑ | PEG-IFN + OCT-LAR 22 | carcinoma | low – intermediate; advanced (unresectable or metastatic) | Yao JC. (65) |
| bFGF ↓ | PEG-IFN + OCT-LAR 22 | carcinoma | low – intermediate; advanced (unresectable or metastatic) | Yao JC. (65) |
| IL18 ↑ | BEV + OCT-LAR 22 | carcinoma | low – intermediate; advanced (unresectable or metastatic) | Yao JC. (65) |
| bFGF ↓ | BEV + OCT-LAR 22 | carcinoma | low – intermediate; advanced (unresectable or metastatic) | Yao JC. (65) |
| VEGF ↓ | IFN-α 8 | carcinoma midgut | advanced (metastatic) | von Marschall Z. (66) |

VEGF, vascular endothelial growth factor; sVEGFR, soluble vascular endothelial growth factor receptor; IL, interleukin; SDF-1a, stromal cell-derived factor 1; PIGF, placental growth factor; bFGF, basic fibroblast growth factor; SUN, sunitinib; EVE, everolimus; IFN-α, interferon α; PEG-IFN, pegylated interferon; OCT-LAR, depot long-acting octreotide; BEV, bevacizumab; hNENs, neuroendocrine neoplasms; NET, neuroendocrine tumors; pts, patients.
(PD1) present on the surface of T lymphocytes and its ligand (PD-L1) on the surface of tumoral cells. PD-L1, by binding to PD-1, activate an inhibitory signal that avoids the destruction of cancer cells by host immune system.

In oncology, several compounds have been developed that act on this mechanism, and they are defined as Immune Checkpoint Inhibitors (ICIs). ICIs are monoclonal antibodies that bind to PD-1 (as Nivolumab and Pembrolizumab) or PD-L1 (as Atezolizumab, Avelumab and Durvalumab), respectively. The outcome of both bonds is to prevent the interaction between PD-1 and PD-L1 from blocking the T lymphocytes capable of attacking and eliminating tumour cells.

Immunotherapy acting through inhibition of PD1 and PD-L1 was firstly introduced with encouraging results in melanoma and non-small cell lung carcinomas (NSCLC), by using nivolumab and pembrolizumab, and now its use is widening in many other malignant tumors (72). To date, tissue expression of PD-L1 is tested by immunohistochemistry (IHC) and evaluated by microscopic assessment in all non-operative NSCLC, where the rate of expression in neoplastic cells can predict treatment response and its efficacy, indicating the place of pembrolizumab in the therapeutic algorithm (73, 74).

In the context of NENs, the potential efficacy of ICIs was investigated, at first, in HG, poorly differentiated NEC. HG-NEC are aggressive tumors, associated with a dismal prognosis (of approximately 10–12 months). The standard of care for this subgroup, still remains chemotherapy, which is associated with rapid but not long-lasting responses. Unfortunately, no targeted agents nor innovative approaches have been validated for NEC, so far. However, a rationale for the use of PD1 and PD-L1 inhibitors in this setting exists and it is represented by their high tumor mutational burden (TMB) (above all of SCLC), if compared to other type of cancer. Therefore, different ICIs have been tested in HG-NEC, confirming their activity. Some key examples are represented by skin Merkel cell carcinoma and SCLC, which almost always do not achieve durable remission with chemo- and radiotherapy, while the introduction of new therapies showed excellent and more durable responses (75, 76). In both cases, Merkel cell carcinoma and SCLC, ICIs have been approved and are currently used in daily clinical practice (77, 78).

However, the optimal selection of patients with HG-NEC as candidate for PD1 and PD-L1 inhibitors is still debated and immunohistochemical evaluation may not be alone satisfactory (76, 79–81).

On the other hand, for well-differentiated, low-grade NET, given their nature of more indolent tumors, with a very low TMB, and considering their relative favorable prognosis in the majority of cases, the potential activity of immune-checkpoint inhibition has not been established, so far. The current guidelines recommend surgery as the only curative treatment for early stages. For locally advanced inoperable or metastatic patients, depending on some essential clinic-pathologic features of each case (primary tumor localization, expression of somatostatin receptors on cell surface, ki67 value, presence of symptoms and tumor burden), the therapeutic armamentarium includes a great variety of active treatments as SSA (Octreotide or Lanreotide), targeted agents (i.e. the mTOR inhibitor EVE and the anti-angiogenetic drug SUN), peptide receptor radionuclide therapy (PRRT) or chemotherapy (82). All these treatments could be used individually or combined, and their sequence is decided case by case within the multidisciplinary-NEN dedicated tumor boards. However, the potential activity of ICIs in NET is still an open and challenging issue and hopefully the results of the studies currently ongoing in this field, could allow to define a role for this strategy.

Clinical Evidence in NEN

As previously reported, a role for ICIs in HG-NEN is a promising therapeutic weapon. Unfortunately, no predictive biomarkers of response to anti-PD1/PDL1 therapy, have been established yet. It is well known that tissue expression and tissue localization (membrane of tumor cells or tumor-infiltrating immune cells, TILs) are both important for the access to the therapy (83). Therefore, the predictive value of PD-L1 expression in tumor cells and TILs by IHC has been investigated within several clinical trials for ICIs, for which different assays with specific IHC platforms were used. Of these, different PD-L1 IHC assays have been validated for the corresponding ICI. Not all laboratories, however, are equipped with dedicated platforms, and many laboratories are used to prepare house assays. Additionally, has been showed that the different available antibodies anti PD-L1 for IHC use are highly heterogeneous in their sensitivity to tumor cells expression or to TILs (83).

In this context, several authors have published results of PD-L1 tissue expression in lung NENs in the last years. The available data are summarized in Table 3. We will comment some of the most relevant papers, on lung NENs (84–90, 95, 96) as well as in Merkel cell carcinoma (92). In 2015, Schultheis and colleagues, were the first who investigated PD-1 and PD-L1 IHC expression in 61 SCLC. No expression in cancer cells was detected.

In 2017, Inamura reported a PD-L1 positivity in 25 cases (21%) of a population of 74 SCLC and 41 LCNEC. The multivarient analysis confirmed PD-L1 expression on tumoral cells as an independent positive prognostic factor (HR=0.29; p=0.006) in lung HG-NENs. In 2018, Eichhorn and colleagues performed a retrospective analysis of PD-L1 expression by IHC in tumoral cells and microenvironment, in a population of 76 LCNECs. The authors found positivity for PD-L1 (positivity was defined as the presence of PD-L1 in >1% of cells) only in tumor cells in 17 cases and only in the tumor microenvironment in 16 cases, while in 12 cases PD-L1 was positive in both cell types. An statistically significant difference in survival was observed comparing the cases with PD- L1 positive tumor/negative immune-cell infiltrate and PD- L1 negative tumor/positive immune-cell infiltrate, being the first associated with a worse prognosis (5-year Tumor-specific survival, TSS: 0% vs. 60%; p < 0.017). This observation was confirmed in 2019, by Xu Y, who reported that PD-L1 expression on tumoral cells was as an independent prognostic factor for OS (HR=2.55, p =0.017) in a population of 60 SCLC patients. The same conclusions came from a more recent study, published in 2020 by Sun C and his colleagues. This analysis included 102 surgically removed stage I,
II and III SCLC. 40.2% and 37.3% of cases were detected to present a positivity on TILs for PD-1 and PD-L1, respectively. Only 3.9% of tumor cells resulted positive for PD-L1. TILs positive cases for PD-L1 presented better RFS (p=0.004). In the same direction, Fan Y. et al. demonstrated that the expression of PD1 in TILs was independently associated with OS (HR 0.367, p=0.001).

**Figure 1** shows a case of SCLC, followed at the Department of Advanced Diagnostic-therapeutic technologies and health services Section of Anatomic Pathology (A. Cardarelli Hospital, Naples, Italy), where PD-L1 positivity was limited to TIL, while tumor cells were negative (Figure 1).

Among Merkel cell carcinoma, in a very interesting study 39 patients were analyzed for immunohistochemical PD-1, PD-L1 and nerve growth factor (NGF) expression. These variables were correlated with clinic and pathological features, showing that PD-L1 and NGF are co-expressed on spindle cells in the microenvironment. Authors suggested that this co-expression might be a link of the microenvironment to the tropomyosin receptor kinase A (TrkA)-positive tumor cells, representing a critical mechanism for tumor growth and lack of response to anti-PD-1/L1 treatment, requiring to be investigated in further studies (91). Another study, by Giraldo et al., included 26 advanced Merkel cell carcinomas and investigated PD-1 and PD-L1 expression in order to determine their role as predictive biomarkers of response to ICIs. In this case, all the patients received treatment with Pembrolizumab. Higher density of expression on tumoral cells for PD-1 (median cells/mm², 70.7 vs 6.7, p=0.03) and PD-L1 (855.4 vs 245.0, p=0.02) in responders versus not responders to pembrolizumab.

**TABLE 3 | Prognostic values of programmed cell death protein 1 receptor (PD1) and programmed death-ligand 1 (PD-L1) in NENs patients.**

| Author, year | Number of patients | Diagnosis | Tumor Grade | Metastasis | PD1/PDL1 and patients outcome |
|-------------|-------------------|-----------|-------------|------------|----------------------------|
| **Lung origin** | | | | | |
| Fan et al. (84) | 80 | 22 NET, 48 SCLC, 10 LCNEC | 1-2-3 | Metastatic & Non-metastatic | The expression of PD1 in TILs was independently associated with OS (HR 0.367, p=0.001) |
| Kim et al. (85) | 192 | 120 SCLC, 72 LCNEC | 3 | Metastatic & Non-metastatic | No relationship between PD-L1 expression on TCs and survival. Patients with PD-L1 expression on TILs had longer PFS than those without PD-L1 expression on TILs (11.3 vs 7.0 months, p=0.02) |
| Kasajima et al. (86) | 242 | 57 NET, 127 SCLC, 58 LCNEC | 1-2-3 | Metastatic & Non-metastatic | For SCLC/LCNEC patients: PD-L1 positivity in TILs correlated with prolonged OS (p<0.01, HR 0.4) |
| Inamura et al. (87) | 115 | 74 SCLC and 41 LCNEC | 3 | Metastatic & Non-metastatic | PD-L1 expression on TCs was an independent positive prognostic factor (p=0.0006, HR=0.29) |
| Eichhorn et al. (88) | 76 | 26 NEC, 50 LCNEC | 3 | Metastatic & Non-metastatic | PD-L1 expression on TCs and negative on TILs was associated with a worse prognosis (6-year TSS: 0% vs 60%; p=0.017) |
| Xu Y. et al. (89) | 60 | SCLC | 3 | Non-metastatic | PD-L1 expression on TCs was a negative independent prognostic factor for OS (HR=2.55, p=0.017) |
| Sun C. et al. (90) | 102 | SCLC | 3 | Non-metastatic | PD-L1 positive on TILs was associated with better RFS (p=0.004) |
| **Merkel cell carcinoma** | | | | | |
| Wehkamp et al. (91) | 39 | NEC | 3 | Metastatic & Non-metastatic | Shorter mOS for PD-1 positive patients (23.2 months vs 61.6 months, p=0.35); shorter mOS for PD-L1+ patients (PD-L1+ 24.7 vs PD-L1- 61.6 months, p=0.88) |
| Giraldo et al. (92) | 26 | NEC | 3 | Metastatic | Higher density of expression on tumoral cells for PD-1 (median cells/mm², 70.7 vs 6.7, p=0.03) and PD-L1 (855.4 vs 245.0, p=0.02) in responders versus not responders to pembrolizumab |
| **GEP origin** | | | | | |
| Wang et al. (93) | 120 | NENs | 1-2-3 | Metastatic & Non-metastatic | PD-L1 resulted an independent prognostic factor for OS |
| Botsch et al. (94) | 244 | NENs | 1-2-3 | Metastatic & Non-metastatic | PD-1 positive vs negative (44.5 months vs 53.8) and PD-L1 positive vs negative (46 months vs 51.9) had a negative impact on OS (p<0.05, in both cases) |

GEP, gastro-entero-pancreatic; HR, hazard ratio; LCNEC, large cell neuroendocrine lung carcinomas; NEC, neuroendocrine carcinomas; NENs, neuroendocrine neoplasms; NET, neuroendocrine tumors; NS, not specified; mOS, median overall survival; OS, overall survival; PFS, progression free survival; SCLC, small cell lung carcinomas; RFS, relapse free survival; TILs, tumor-infiltrating lymphocytes; TCs, tumor cells; TSS, tumor-specific survival; vs, versus.
Among GEP-NEN, only few studies about the evaluation of PD-L1 by IHC have been published so far. In 2017, Cavalcanti and colleagues, studied the expression of this tissue marker in 57 G1, G2 and G3 extrapulmonary-NENs (85, 97, 98). The authors found a significant correlation between PD-L1 expression by tumor cells and immune infiltrates and G3 of WHO classification (p=0.001), while it was not associated with gender, primary site, or number of metastatic sites. The next year, Lamarca et al., evaluated PD-L1 expression in 62 well-differentiated, G1 or G2 Si-NETs. PD-L1 was studied in tumoral cells as well as in TILs (85, 97, 98). PD-L1 expression was positive in 12.8% of cases and in 24.3% of TILs. PD-1 was expressed in 22.8% of TILs. Furthermore, the results obtained by IHC were confirmed with RT-qPCR. This technique detected higher expression levels of PD-L1 (p=0.007) and PD-1 (p=0.001) in samples positive by IHC compared to negative by IHC. In 2019, Wang and colleagues (93), investigated the positivity for PD-1/PD-L1 in 120 GEP-NENs. In this study, PD-L1 was expressed in 52.5% of the tumor cells, while PD-L1 was positive in 55.8% of TILs. At multivariate analysis, PD-L1 resulted an independent prognostic factor in this population. Additionally, Bösch and colleagues, included 244 pancreatic and G1, G2 and G3 SI-NEN patients (94). In this study, PD-1/PD-L1 were analysed on TILs, where a high PD-1 expression was demonstrated in 35 samples (16.1%), and a high PD-L1 expression was evidenced in 20 cases (8.7%). A significant negative impact on OS for PD-1 and PD-L1 positivity was demonstrated (p< 0.05, in both cases).

Future Directions
The rationale of investigating PD-1 and PD-L1 expression in NENs is represented by the clinical need to find predictive biomarkers of response to ICIs. However, the role of PD-1 and PD-L1 tissue testing (in tumoral cells as well as in TILs) in defining the access to immunotherapy in NENs is still uncertain (87, 96).

The majority of the available supporting data are in the field of HG-NEN, as previously reported in detail. To date, skin Merkel cell carcinoma should be considered a paradigm for the efficacy of immunotherapy in NENs. However, PD-1 and PD-L1 tissue testing has not been validated as a fundamental predictive marker for patients selection (75). Also, in SCLC ICIs treatment has been approved, but even in this case the debate regarding predictive biomarkers of response is still an open issue (76). Among GEP-NEN, only a couple of studies have been carried on. Taking all the results together, PD-1 and PD-L1 expression appear to possibly have a role as negative prognostic biomarkers. However, further prospective studies, aimed to determine the epidemiology and the role as predictive or prognostic markers in NENs should be highly encouraged.

CONCLUSIONS
NENs are a complex family of tumors, extremely heterogeneous in terms of primary origin of the tumor, tumor morphology (from well differentiated to poorly differentiated forms), proliferation index, clinical presentation and prognosis. To date, several treatments are available for NENs, including SSA, PRRT, targeted agents, chemotherapy, surgery and locoregional approaches. However, despite a clear role for inflammation in cancer and in NENs, only few immunotherapy agents have been approved (mainly in Merkel cell carcinoma and in SCLC) and
above all no specific biomarkers capable of early predicting response to these agents, have been validated so far.

NLR and PLR and pro-inflammatory cytokines could represent a new tool for the early management of NENs. However, future studies adopting a prospective and matched study design need to confirm the role of inflammatory markers in NENs diagnosis, response evaluation, prognosis, and follow-up.

In conclusion, this panel of circulating inflammatory markers, correlated where possible with tissue markers, may be of utility if integrated in a cluster as biomarkers for targeted therapies response in clinical practice.

**AUTHOR CONTRIBUTIONS**

EG, AS, LR, GM, SC, and AF selected the issue, researched studies from databases, and independently analyzed published data. EG, AS, LR, GM, SC, CP, and AF contributed to the final version of the manuscript. EG, CP, and AF performed quality control checks on extracted data. AC verified the analytic method and supervised the planned literature review of literature. SC conceived the issue, researched and approved the submitted version.

**REFERENCES**

1. Landskron G, de la Fuente M, Thuwajit P, Thuwajit C, Hermoso MA. Chronic Inflammation and Cytokines in the Tumor Microenvironment. *J Immunol Res* (2014) 2014:149185. doi: 10.1155/2014/149185

2. Mostofa AG, Punganuru SR, Madala HR, Al-Obaide M, Srivenugopal KS. The Process and Regulatory Components of Inflammation in Brain Oncogenesis. *Biomolecules* (2017) 7(2):34. doi: 10.3390/biom7020034

3. Yu S, Wang Y, Jing L, Claret FX, Li Q, Tian T, et al. Autophagy in the “Inflammation-Carcinogenesis” Pathway of Liver and HCC. Immunotherapy. *Cancer Lett* (2017) 411:82–9. doi: 10.1016/j.canlet.2017.09.049

4. Raja UM, Gopal G, Shirley S, Ramakrishnan AS, Rajkumar T. Cells of High-Grade Neuroendocrine Carcinomas of the Lung. *J Cancer Res Clin Oncol* (2013) 139(11):1869–78. doi: 10.1007/s00432-013-1502-5

5. Liepelt A, Tacke F. Stromal Cell-Derived Factor-1 (SDF-1) as a Target in Liver Diseases. *Am J Physiol Gastrointestinal liver Physiol* (2016) 311(2):G203–9. doi: 10.1152/ajpgi.00193.2016

6. Elia G, Fallahi P. Hepatocellular carcinoma and CXCR3: Chemokines: A Narrative Review. *La Clin Terapeutica* (2017) 168(1):e37–41. doi: 10.7417/CT.2017.1980

7. Altundag O, Altundag K, Morandi P, Gunduz M. Cytokines and Chemokines as Predictive Markers in non-Small Cell Lung Cancer Patients With Brain Metastases. *Lung Cancer* (2005) 47(2):291–2. doi: 10.1016/j.lungcan.2004.09.003

8. Lukasiewicz-Zajac M, Mroczoł B, Smitkowski M. Chemokines and Their Receptors in Esophageal Cancer—the Systematic Review and Future Perspectives. *Tumour Biol* 41. doi: 10.1159/000445045

9. King J, Mir H, Singh S. Association of Cytokines and Chemokines in Pathogenesis of Breast Cancer. *Prog Mol Biol Trans Sci* (2017) 151:113–36. doi: 10.1016/bs.pmbts.2017.07.003

10. Mukherjeer S, Siddiqui MA, Dayal S, Ayoub YZ, Malathi K. Epigallocatechin-3-Gallate Suppresses Proinflammatory Cytokines and Chemokines Induced by Toll-Like Receptor 9 Agonists in Prostate Cancer Cells. *J Inflammation Res* (2014) 7:89–101. doi: 10.2147/JIR.S61365

11. Samarendra H, Jones K, Petrinic T, Silva MA, Reddy S, Soonawalla Z, et al. A Meta-Analysis of CXCL12 Expression for Cancer Prognosis. *Br J Cancer* (2017) 117(1):124–35. doi: 10.1038/bjc.2017.134

12. Takahashi A, Ishii G, Kinoshita T, Yoshida T, Umemura S, Hishida T, et al. Identification of Prognostic Immunophenotypic Features in Cancer Stroma Cells of High-Grade Neuroendocrine Carcinomas of the Lung. *J Cancer Res Clin Oncol* (2013) 139(11):1869–78. doi: 10.1007/s00432-013-1502-5

13. Raja UM, Gopal G, Shirley S, Ramakrishnan AS, Rajkumar T. Cells of High-Grade Neuroendocrine Carcinomas of the Lung. *J Cancer Res Clin Oncol* (2013) 139(11):1869–78. doi: 10.1007/s00432-013-1502-5

14. Franco AT, Cokken A, Waj J, Platelets at the Interface of Thrombosis, Inflammation, and Cancer. *Blood* (2015) 126(5):582–8. doi: 10.1182/blood-2014-08-531582

15. Arima K, Okabe H, Hashimoto D, Chikamoto A, Nitta H, Higashi T, et al. Neutrophil-To-Lymphocyte Ratio Predicts Metachronous Liver Metastasis of Pancreatic Neuroendocrine Tumors. *Int J Clin Oncol* (2017) 22(4):734–9. doi: 10.1186/s10147-017-1111-4

16. Cao LL, Lu J, Lin JX, Zheng CH, Li P, Xie JW, et al. A Novel Predictive Model Based on Preoperative Blood Neutrophil-to-Lymphocyte Ratio for Survival Prognosis in Patients With Gastric Neuroendocrine Neoplasms. *Oncotarget* (2016) 7(27):20455–58. doi: 10.18632/oncotarget.9805

17. Vujovic A, Cigrovski Berkovic M, Cacev T, Catela Ivkovic T, Zjacic-Rotkvic V, et al. Predictive Markers in non-Small Cell Lung Cancer Patients With Brain Metastases. *Clin Oncol* (2016) 28(6):261–6. doi: 10.1159/000445045

18. Ruszniewski P, Delle Fave G, Chikamoto A, Nitta H, Higashi T, et al. Neutrophil-To-Lymphocyte Ratio Predicts Metachronous Liver Metastasis of Pancreatic Neuroendocrine Tumors. *Int J Clin Oncol* (2017) 22(4):734–9. doi: 10.1186/s10147-017-1111-4

19. Cigrovski Berkovic M, Cacev T, Catela Ivkovic T, Zjacic-Rotkvic V, et al. Predictive Markers in non-Small Cell Lung Cancer Patients With Brain Metastases. *Clin Oncol* (2016) 28(6):261–6. doi: 10.1159/000445045

20. Le Marc H, Bost F, Pouc M, Roux J, Pasquier D, Pasquier B. Carcinoid Tumour Complicating Inflammatory Bowel Disease. A Study of

**FUNDING**

Ministerial research project PRIN2017Z3N3YC

**ACKNOWLEDGMENTS**

This review is part of the ‘NIKE’ project (Neuroendocrine tumors Innovation Knowledge and Education) led by Prof Annamaria Colao and Dr Antongiulio Faggiano, which aims at increasing the knowledge on NETs. We would like to acknowledge all the Collaborators of this project: Albertelli M. (Genova), Bianchi A. (Roma), Ciricelli L. (Napoli), De Cicco F. (Napoli), Dicitore A. (Milano), Di Dato C. (Roma), Di Molfetta S. (Bari), Fanciulli G. (Sassari), Ferraiu F. (Messina), Gallo M. (Torino), Grossrubatscher E. (Milano), Guadagno V. (Napoli), Guarnotta V. (Palermo), Lo Calzo F. (Napoli), Kara E. (Udine), Malandrino P. (Catania), Messina E. (Messina), Modica R. (Napoli), Pisa G. (Napoli), Razzore P. (Torino), Rubino M. (Milano), Ruggeri R.M. (Messina), Sciammarella C. (Napoli), Vitala G. (Milano), Zatelli M.C. (Ferrara). We would like to thank Marie-Hélène Hayles for revision of the English text. We wish to thank the NETTARE Unit—NeuroEndocrine Tumor TAsk foReC “Sapienza” University of Rome, Italy, led by Prof. Andrea Lenzi, Prof. Antongiulio Faggiano, Prof. Elisa Giannetta and Prof. Andrea M. Isidori.
Two Cases With Review of the Literature. *Pathol Res Pract* (1994) 190 (12):1185–92; discussion 93–200. doi: 10.1016/S0344-0338(11)80445-0

21. Cadle S, Johnson BT, Turner G, McCanne D, Ardill J, McGinty A. An Evaluation of Cyclooxygenase-2 as a Prognostic Biomarker in Mid-Gut Carcinoid Tumours. *Neuroendocrinology* (2007) 86(2):104–11. doi: 10.1159/000107555

22. Dolan RD, McSorley ST, Horgan PG, Laird B, McMillan DC. The Role of the Systemic Inflammatory Response in Predicting Outcomes in Patients With Advanced Inoperable Cancer: Systematic Review and Meta-Analysis. *Crit Rev Oncol Hematol* (2017) 116:134–46. doi: 10.1016/j.critrevonc.2017.06.002

23. Guthrie GJ, Charles KA, Rooburgh CS, Horgan PG, McMillan DC, Clarke SJ. The Systemic Inflammation-Based Neutrophil-Lymphocyte Ratio: Experience in Patients With *Cancer*. Crit Rev Oncol Hematol (2013) 88(1):218–30. doi: 10.1016/j.critrevonc.2013.03.010

24. Templeton AJ, Ace O, McNamara MG, Al-Mubarak M, Vera-Badillo FE, Hermanns T, et al. Prognostic Role of Platelet to Lymphocyte Ratio in Solid Tumors: A Systematic Review and Meta-Analysis. *Cancer Epidemiol Biomarkers Prev* (2014) 23(7):1204–12. doi: 10.1158/1055-9966.EPI-14-0146

25. McMillan DC. The Systemic Inflammation-Based Glasgow Prognostic Score: A Decade of Experience in Patients With Cancer. *Cancer Treat Rev* (2013) 39 (5):534–40. doi: 10.1016/j.ctrv.2012.08.003

26. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-Related Inflammation. *Nature* (2004) 431(7006):356–40. doi: 10.1038/nature02930

27. Zhou B, Deng J, Chen L, Zheng S. Preoperative Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio in Resectable Pancreatic Neuroendocrine Tumors (PNETs) in the Head After Curative Resection. *BMJ Endocr Disord* (2019) 19(1):123. doi: 10.1186/s12920-019-0454-4

28. Liu Y, Yuan Y, Li Y, Zhang J, Xiao G, Vodovoz Y, et al. Interacting Neuroendocrine and Inmate and Acquired Immune Pathways Regulate Neutrophil Mobilization From Bone Marrow Following Hemorrhagic Shock. *J Immunol* (2009) 182(1):572–80. doi: 10.4049/jimmunol.182.1.572

29. Grivennikov SI, Getren FR, Karin M. Immunity, Inflammation, and Cancer. *Cell* (2010) 140(6):883–99. doi: 10.1016/j.cell.2010.01.025

30. Huang S. Regulation of Metastases by Signal Transducer and Activator of Transcription 3 Signaling Pathway: Clinical Implications. *Clin Cancer Res: Off J Am Assoc Cancer Res* (2007) 13(5):1362–6. doi: 10.1158/1078-0432.CCR-06-2313

31. Naugler WE, Karin M. NF-kappaB and Cancer: Identifying Targets and Mechanisms. *Curr Opin Genet Dev* (2008) 18(1):19–26. doi: 10.1016/j.gde.2008.01.020

32. Liu Y, Zheng J, Zhang D, Jing L. Neutrophil-Lymphocyte Ratio and Plasma Lactate Predict 28-Day Mortality in Patients With Sepsis. *J Clin Lab Anal* (2019) 33(7):e22942. doi: 10.1002/jcla.22942

33. Tong Z, Liu L, Zheng Y, Jiang W, Zhao P, Fang W, et al. Predictive Value of Preoperative Peripheral Blood Neutrophil/Lymphocyte Ratio for Lymph Node Metastasis in Patients of Resectable Pancreatic Neuroendocrine Tumors: A Nomogram-Based Study. *World J Surg Oncol* (2017) 15(1):108. doi: 10.1186/s12957-017-1169-5

34. Zhou B, Zhan C, Wu J, Liu J, Zhou J, Zheng S. Prognostic Significance of Preoperative Neutrophil-to-Lymphocyte Ratio in Surgically Resectable Pancreatic Neuroendocrine Tumors. *Med Sci Monit* (2017) 23:5574–88. doi: 10.12659/MSM.907182

35. Zhou B, Deng J, Chen L, Zheng S. Preoperative Neutrophil-to-Lymphocyte Ratio and Tumor-Related Factors to Predict Lymph Node Metastasis in Nonfunctioning Pancreatic Neuroendocrine Tumors. *Sci Rep* (2017) 7(1):17506. doi: 10.1038/s41598-017-17885-y

36. Okui M, Yamamichi T, Asakawa A, Harada M, Saito M, Hiroi H. Prognostic Significance of Neutrophil-Lymphocyte Ratios in Large Cell Neuroendocrine Carcinoma. *Gen Thorac Cardiovasc Surg* (2017) 65(11):633–9. doi: 10.1007/s11748-018-0804-y

37. Gaitanidis A, Patel D, Nilubol N, Tirosch A, Sadowski S, Kebebew E. Markers of Systemic Inflammatory Response are Prognostic Factors in Patients With Pancreatic Neuroendocrine Tumors (PNETs): A Prospective Analysis. *Ann Surg Oncol* (2018) 25(1):122–30. doi: 10.1245/s10434-017-6241-4

38. McDermott SM, Saunders ND, Schneider EB, Strosberg D, Onesti J, Dillhoff M, et al. Neutrophil Lymphocyte Ratio and Transarterial Chemoembolization in Neuroendocrine Tumor Metastases. *J Surg Res* (2018) 232:369–75. doi: 10.1016/j.jss.2018.08.058

39. Zou J, Li Q, Kou F, Zhu Y, Lu M, Li J, et al. Prognostic Value of Inflammation-Based Markers in Advanced or Metastatic Neuroendocrine Tumors. *Curr Oncol* (2019) 26(1):e30–e8. doi: 10.3747/cao.2017.26.4135

40. Panni RZ, Lopez-Aguilar AG, Liu J, Poultides GA, Rocha FG, Hawkins WG, et al. Association of Preoperative Monocyte-to-Lymphocyte and Neutrophil-to-Lymphocyte Ratio With Recurrence-Free and Overall Survival After Resection of Pancreatic Neuroendocrine Tumors (US-NETSG). *J Surg Oncol* (2019) 120(4):632–8. doi: 10.1002/jso.25629

41. Harimoto N, Hoshino K, Murauchi R, Hagikura K, Yamakana T, Ishii N, et al. Prognostic Significance of Neutrophil-Lymphocyte Ratio in Resectable Pancreatic Neuroendocrine Tumors With Special Reference to Tumor-Associated Macrophages. *Pancreatology* (2019) 19(6):897–902. doi: 10.1016/j.pan.2019.08.003

42. Pozza A, Pauletta B, Scarpa M, Ruffolo C, Bassi N, Massani M. Prognostic Role of Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio in Patients With Midgut Neuroendocrine Tumors Undergoing Resective Surgery. *Int J Colorectal Dis* (2019) 34(11):1849–56. doi: 10.1007/s00384-019-03356-5

43. Zhou B, Zhan C, Xiang J, Ding Y, Yan S. Clinical Significance of the Prooperative Main Pancreatic Duct Dilation and Neutrophil-to-Lymphocyte Ratio in Pancreatic Neuroendocrine Tumors (PNETs) of the Head After Curative Resection. *BMJ Endocr Disord* (2019) 19(1):123. doi: 10.1186/s12920-019-0454-4
Neuroendocrine Carcinoma of the Lung. *J Cancer Res Clin Oncol* (2016) 142 (5):905–12. doi: 10.1007/s00432-015-2098-8

58. Cella CA, Minucci S, Spada F, Galdy S, Elgindy M, Ravnenda PS, et al. Dual Inhibition of mTOR Pathway and VEGF Signalling in Neuroendocrine Neoplasms: From Bench to Bedside. *Cancer Treat Rev* (2015) 41(9):754–60. doi: 10.1016/j.ctrv.2015.06.008

59. Plev ME, Hassler G, Baum U, Hahn EG, Lohmann T, Schuppan D. Circulating Levels of Angiogenic Cytokines can Predict Tumour Progression and Prognosis in Neuroendocrine Carcinomas. *Clin Endocrinol* (2005) 62(4):434–43. doi: 10.1111/j.1365-2265.2005.02238.x

60. Faivre S, Delbado C, Vera K, Robert C, Lozahic S, Lasau N, et al. Safety, Pharmacokinetic, and Antitumor Activity of SU11248, a Novel Oral Multitarget Tyrosine Kinase Inhibitor, in Patients With Cancer. *J Clin Oncol: Off J Am Soc Clin Oncol* (2006) 24(1):25–35. doi: 10.1200/JCO.2005.22.2194

61. Bello CDSE, Fricce I, Smeraglia J, Sherman L, TycE, Baum L, Metropol NJ, et al. Analysis of Circulating Biomarkers of Sunitinib Malate in Patients With Unresectable Neuroendocrine Tumors (NET): VEGF, IL-8, and Soluble VEGF Receptors 2 and 3. *J Clin Oncol* (2006) 4045(18_suppl.). doi: 10.1200/jco.2006.24.18_suppl.4045

62. Huang D, Ding Y, Zhou M, Rini BI, Petillo D, Qian CN, et al. Interleukin-8 (CXCL8) is Required for IL-8/CXCL8-Induced Endothelial Permeability. *Chemokines Modulate the Tumour Microenvironment in Pituitary Carcinoma*. *Mol Cancer Ther* (2017) 16(11):2486. doi: 10.1158/1535-7189.MCT-17-0241

63. Gung J, Chehrazi-Rafale A, Reddi S, Salga R, Development of PD-1 and PD-L1 Inhibitors as a Form of Cancer Immunotherapy: A Comprehensive Review of Registration Trials and Future Considerations. *J Immunother Cancer* (2018) 6(1):8. doi: 10.1186/s40423-018-0351-z

64. Fusi A, Festino L, Botti G, Masucci G, Melero I, Lorigan P, et al. PD-L1 Expression as a Potential Predictive Biomarker. *Lancet Oncol* (2015) 16(1):1285–7. doi: 10.1016/S1470-2045(15)03037-0

65. Udall M, Rizzo M, Kenny J, Doherty J, Dahm S, Robbins P, et al. PD-L1 Diagnostic Tests: A Systematic Literature Review of Scoring Algorithms and Test-Validation Metrics. *Diag Pathol* (2018) 13(1):12. doi: 10.1186/s13000-018-0689-9

66. Palla AR, Doll D. Immunotherapy in Merkel Cell Carcinoma: Role of Avelumab. *Immunother Targets* (2018) 7:15–9. doi: 10.2147/IT.S135563

67. Saito M, Shiraiishi K, Goto A, Suzuki H, Kohno T, Kono K. Development of Targeted Therapy and Immunotherapy for Treatment of Small Cell Lung Cancer. *Jpn J Clin Oncol* (2018) 48(7):603–8. doi: 10.1093/jjco/hyy068

68. Femia D, Prinzi N, Anichini A, Mortarini R, Nichetti F, Corti F, et al. Treatment of Advanced Merkel Cell Carcinoma: Current Therapeutic Options and Novel Immunotherapy Approaches. *Target Oncol* (2018) 13(5):567–82. doi: 10.1007/s11523-018-0585-y

69. Yang S, Zhang Z, Wang Q. Emerging Therapies for Small Cell Lung Cancer. *J Hematol Oncol* (2019) 12(1):47. doi: 10.1186/s13045-019-0736-3

70. Gadgeel SM, Pennell NA, Filidjer MJ, Halmos B, Bonomi P, Stevenson J, et al. Phase II Study of Maintenance Pembroliuzumab in Patients With Extensive-Stage Small Cell Lung Cancer (SCLC). *J Thorac Oncol: Off Publ Int Assoc Study Lung Cancer* (2018) 13(9):1393–9. doi: 10.1016/j.jtho.2018.05.002

71. Pakkala S, Oononokoko TK. Immune Checkpoint Inhibitors in Small Cell Lung Cancer. *J Thorac Dis* (2018) 10(Suppl 3):S455–S467. doi: 10.21037/jtd.2017.12.51

72. Weber MM, Fottner C. Immune Checkpoint Inhibitors in the Treatment of Patients With Neuroendocrine Neoplasia. *Oncol Res Treat* (2018) 41(5):306–12. doi: 10.1159/000488996

73. Patel M, Valle JW, Eriiksson B, Rinke A, Caplin M, Chen J, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasms: Systemic Therapy - Biotherapy and Novel Targeted Agents. *Neuroendocrinology* (2017) 105(3):266–80. doi: 10.1159/000471880

74. Sholl LM, Aisner DL, Allen TC, Beasley MB, Borczuk AC, Cagle PT, et al. Programmed Death Ligand-1 Immunochemistry—A New Challenge for Pathologists: A Perspective From Members of the Pulmonary Pathology Society. *Arch Pathol Lab Med* (2016) 140(4):341–4. doi: 10.5858/arpc.2015-0506-SA

75. Fan Y, Ma K, Wang C, Ning J, Hu Y, Dong D, et al. Prognostic Value of PD-L1 and PD-1 Expression in Pulmonary Neuroendocrine Tumors. *Onco Targets Ther* (2016) 9:6075–82. doi: 10.2147/OTT.S115054

76. Kim HS, Lee JH, Nam SJ, Ock CY, Moon JW, Yoo CW, et al. Association of PD-L1 Expression With Tumor-Infiltrating Immune Cells and Mutation Burden in High-Grade Neuroendocrine Carcinoma of the Lung. *J Thorac Oncol: Off Publ Int Assoc Study Lung Cancer* (2018) 13(5):636–48. doi: 10.1016/j.jtho.2018.01.008

77. Kasaijuma A, Ishikawa Y, Iwata A, Steiger K, Oka N, Ishida H, et al. Inflammation and PD-L1 Expression in Pulmonary Neuroendocrine Tumors. *Endocr Relat Cancer* (2018) 25(3):339–50. doi: 10.1530/ERC-17-0427

78. Inamura K, Yokouchi Y, Kobayashi M, Ninomiya H, Sakakibara R, Nishio M, et al. Relationship of Tumor PD-L1 (CD274) Expression With Lower Mortality in Lung High-Grade Neuroendocrine Tumor. *Cancer Med* (2017) 6(10):2347–56. doi: 10.1002/cam4.11172

79. Eichhorn F, Harms A, Warth M, Muley T, Winter H, Eichhorn ME. PD-L1 Expression in Large Cell Neuroendocrine Carcinoma of the Lung. *Cancer Med* (2018) 7:1560–69. doi: 10.1002/cam4.2056

80. Xu Y, Cui G, Jiang Z, Li N, Zhang X, Survival Analysis With Regard to PD-L1 Expression in Human Small Cell Lung Cancer and a Comparison With Associated Receptors. *Onco Lett* (2019) 17(3):2960–8. doi: 10.3892/ol.2019.9910

81. Sun C, Zhang Z, Wang L, Yin Y, Chen B, Zhao S, et al. Expression of PD-1 and PD-L1 on Tumor-Infiltrating Lymphocytes Predicts Prognosis in Patients With Small-Cell Lung Cancer. *Onco Targets Ther* (2020) 13:6475–83. doi: 10.2147/OTT.S252031

82. Wehkmann U, Kemp S, Krause C, Weichenthal M, Hauschild A, Rocken C, et al. Co-Expression of NGF and PD-L1 on Tumor-Associated Immune Cells in the Microenvironment of Merkel Cell Carcinoma. *J Cancer Res Clin Oncol* (2018) 144(7):1301–8. doi: 10.1007/s00432-018-2657-x

83. Giraldo NA, Nguyen P, Engle EL, Kaunitz GJ, Cottrell TR, Berry S, et al. Multidimensional, Quantitative Assessment of PD-1/PD-L1 Expression in
Patients With Merkel Cell Carcinoma and Association With Response to Pembrolizumab. *J Immunother Cancer* (2018) 6(1):99. doi: 10.1186/s40425-018-0404-0

93. Wang C, Yu J, Fan Y, Ma K, Ning J, Hu Y, et al. The Clinical Significance of PD-L1/PD-1 Expression in Gastroenteropancreatic Neuroendocrine Neoplasia. *Ann Clin Lab Sci* (2019) 49(4):448–56.

94. Bosch F, Bruwer K, Altendorf-Hofmann A, Auernhammer CJ, Spitzweg C, Westphalen CB, et al. Immune Checkpoint Markers in Gastroenteropancreatic Neuroendocrine Neoplasia. *Endocr Relat Cancer* (2019) 26(3):293–301. doi: 10.1530/ERC-18-0494

95. Tsuruoka K, Horinouchi H, Goto Y, Kanda S, Fujiwara Y, Nokihara H, et al. PD-L1 Expression in Neuroendocrine Tumors of the Lung. *Lung Cancer* (2017) 108:115–20. doi: 10.1016/j.lungcan.2017.03.006

96. Schultheis AM, Scheel AH, Ozretic L, George J, Thomas RK, Hagemann T, et al. PD-L1 Expression in Small Cell Neuroendocrine Carcinomas. *Eur J Cancer* (2015) 51(3):421–6. doi: 10.1016/j.ejca.2014.12.006

97. Cavalcanti E, Armentano R, Valentini AM, Chieppa M, Caruso ML. Role of PD-L1 Expression as a Biomarker for GEP Neuroendocrine Neoplasm Grading. *Cell Death Dis* (2017) 8(8):e3004. doi: 10.1038/cddis.2017.401

98. Lamarca A, Nonaka D, Breitwieser W, Ashton G, Barriuso J, McNamara MG, et al. PD-L1 Expression and Presence of TILs in Small Intestinal Neuroendocrine Tumours. *Oncotarget* (2018) 9(19):14922–38. doi: 10.18632/oncotarget.24464

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

*Copyright © 2021 Giannetta, La Salvia, Rizza, Muscogiuri, Campione, Pozza, Colao and Faggiano. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.*
### Glossary

| Abbreviation | Full Form |
|--------------|-----------|
| bFGF         | basic fibroblast growth factor |
| CAFs         | cancer-associated fibroblasts |
| CEA          | carcinoembryonic antigen |
| CgA          | chromogranin A |
| DFS          | disease-free survival |
| EVE          | everolimus |
| g-NECs       | gastric neuroendocrine neoplasms |
| g-NEC        | gastric neuroendocrine carcinoma |
| g-MANEC      | gastric mixed adenoneuroendocrine carcinoma |
| GEP          | gastroenteropancreatic |
| HG-NEC       | high-grade neuroendocrine carcinomas |
| HR           | hazard ratio |
| ICIs         | Immune Checkpoint Inhibitors |
| IL-1β        | Interleukin 1 beta |
| IL-2         | Interleukin 2 |
| IL-6         | Interleukin 6 |
| IL-8         | Interleukin 8 |
| IL-10        | Interleukin 10 |
| IL-17        | Interleukin 17 |
| IL-18        | Interleukin 18 |
| IHC          | immunohistochemistry |
| ITGB1        | Integrin Subunit Beta 1 |
| LCNEC        | large cell neuroendocrine lung carcinomas |
| MMP-9        | matrix metalloproteinase-9 |
| NECs         | neuroendocrine carcinomas |
| NENs         | neuroendocrine neoplasms |
| NETs         | neuroendocrine tumors |
| NF-kB        | nuclear factor kappa-light-chain-enhancer of activated B cells |
| NLR          | neutrophil-lymphocyte ratio |
| NSCLC        | non-small cell lung carcinomas |
| NGF          | nerve growth factor |
| NSE          | Neuron-specific enolase |
| OS           | overall survival |
| pNENs        | pancreatic NENs |
| pNETs        | pancreatic NETs |
| PiGF         | Placental Growth Factor |
| PD-1         | programmed cell death protein 1 receptor |
| PD-L1        | programmed death-ligand 1 |
| PDGF         | platelet-derived growth factor |
| PFS          | progression-free survival |
| PLR          | platelet-lymphocyte ratio |
| PRRT         | Peptide receptor radionuclide therapy |
| SCLC         | small cell lung carcinomas |
| SSA          | somatostatin analogues inhibitors |
| STAT3        | signal transducer and activator of transcription 3 |
| SDF-1α       | stromal cell-derived factor-1 |
| SUN          | sunitinib |
| RCC          | renal clear-cell carcinomas |
| RFS          | relapse free survival |
| TANs         | tumor-associated neutrophils |
| TACE         | transarterial chemoembolization |
| TEMs         | Tie2-expressing monocytes/macrophages |
| TGFi-β       | Transforming growth factor beta |
| TILs         | tumor-infiltrating immune cells |
| TMB          | tumor mutational burden |
| TNF-α        | tumor necrosis factor |
| TRAIL        | TNF-related apoptosis-inducing ligand |
| TRKA         | tropomyosin receptor kinase A |
| VEGF         | vascular endothelial growth factor |