Cancer Treatment Reviews 146 (2026) 103135

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Tumour Review

Interleukin-8: a tumor-agnostic biomarker integrating cancer biology and host response across solid tumors

Ilaria Mariangela Scaglione [a,1], Chiara Bazzichetto [b,c,1], Michele Borghesani [a], Francesca Zacchi [a], Serena Eccher [a], Marco Sposito [a], Jessica Insolda [a], Elena Giontella [a], Elena Trevisani [a], Alice Avancini [d], Daniela Tregnago [a], Sara Cingarlini [a], Sara Pilotto [a], Fabiana Conciatori [b,c,*], Lorenzo Belluomini [a,2], Michele Milella [a,2,**]

[a] Section of Oncology, Department of Engineering for Innovation Medicine (DIMI), University of Verona School of Medicine and Verona University Hospital Trust, Verona, Italy
[b] Preclinical Models and New Therapeutic Agents Unit, IRCCS Regina Elena National Cancer Institute, 00144 Rome, Italy
[c] Medical Oncology 1, IRCCS Regina Elena National Cancer Institute, 00144 Rome, Italy
[d] Department of Neurosciences, Biomedicine and Movement, University of Verona, Verona, Italy

ARTICLE INFO

Keywords:
Interleukin-8
Gastrointestinal Cancer
Genitourinary cancer
Lung cancer
Melanoma, breast cancer
Ovarian cancer
Head and neck cancer
Immunotherapy
Prognostic/predictive biomarkers

ABSTRACT

Interleukin-8 (IL-8/CXCL8) drives tumor progression via CXCR1/2 signaling, promoting proliferation, invasion, angiogenesis, and recruitment of pro-tumoral immune and stromal cells. Accumulating clinical evidence indicates that elevated circulating or intratumoral IL-8 levels are consistently associated with adverse prognosis and reduced therapeutic benefit across principal solid tumors. In particular, IL-8 has emerged as a promising prognostic and predictive biomarker of resistance to immune checkpoint inhibitors. This review highlights its prognostic and predictive value across gastrointestinal, genitourinary, lung, melanoma, breast, ovarian, and head and neck cancers, and discusses strategies targeting IL-8 and the need for standardized, clinically actionable assays.

Introduction

Interleukin-8 (IL-8, CXCL8) is a pro-inflammatory chemokine originally identified for its role in neutrophil chemotaxis and activation [1]. Strategically positioned at the tumor/host interface, IL-8 regulates multiple aspects of tumor biology and therapeutic resistance across a spectrum of different malignancies [2]. Once released as a soluble factor in the tumor microenvironment (TME), IL-8 acts in an autocrine and paracrine fashion by binding to the CXCR1 and CXCR2 receptors on the surface of tumor, stromal, and immune cells; downstream-activated pathways, like the canonical MAPK and PI3K cascades, in turn, orchestrate many biological functions in the tumor and stromal/immune compartments, resulting in an aggressive cancer behaviour [3] (Fig. 1).

The *IL-8* gene, located at 4q12-q13, presents over 700 single nucleotide polymorphisms (SNPs), such as − 251 T/A (rs4073), +781C/T (rs2227306), +1633C/T (rs2227543) and + 2767 A/T (rs1126647), occurring in both coding and non-coding regions. Although results are not always consistent across studies, non-coding IL8 variants are generally associated with altered susceptibility or outcome in inflammatory, infectious, and neoplastic diseases (Table 1), through altered

* Corresponding author at: Preclinical Models and New Therapeutic Agents Unit, IRCCS Regina Elena National Cancer Institute, 00144 Rome, Italy.
** Corresponding author at: Section of Innovation Biomedicine - Oncology Area, Department of Engineering for Innovation Medicine (DIMI), University of Verona, P. le L.A. Scuro 10, 37134 Verona, Italy.
E-mail addresses: ilariascaglione90@gmail.com (I.M. Scaglione), chiara.bazzichetto@ifo.it (C. Bazzichetto), borghesanimichele@gmail.com (M. Borghesani), francesca.zacchi@univr.it (F. Zacchi), sr.eccher@gmail.com (S. Eccher), marcosposito91@gmail.com (M. Sposito), jessica.insolda@univr.it (J. Insolda), giontelena@gmail.com (E. Giontella), elenatrevi.et@gmail.com (E. Trevisani), alice.avancini@univr.it (A. Avancini), daniela.tregnago_01@univr.it (D. Tregnago), sara.cingarlini@aovr.veneto.it (S. Cingarlini), sara.pilotto@univr.it (S. Pilotto), fabiana.conciatori@ifo.it (F. Conciatori), lorenzo.belluomini@univr.it (L. Belluomini), michele.milella@univr.it (M. Milella).
[1] Equally contributed (these authors share first co-authorship).
[2] Equally contributed (these authors share last co-authorship).

https://doi.org/10.1016/j.ctrv.2026.103135
Received 7 February 2026; Received in revised form 9 April 2026; Accepted 10 April 2026
Available online 14 April 2026

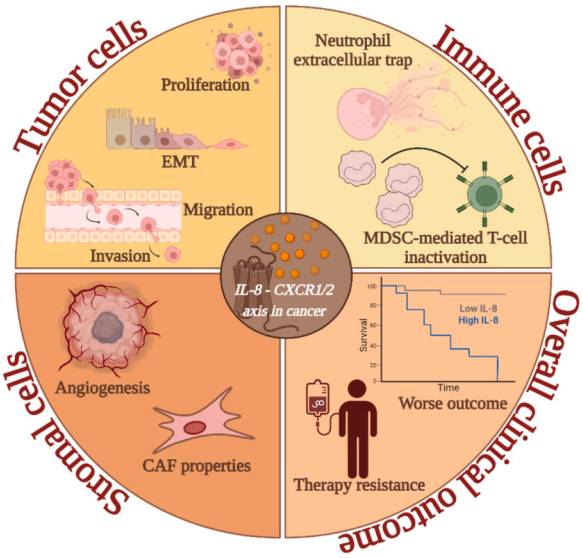

Fig. 1. IL-8 CXCR1/2 axis in cancer – IL-8, released into the tumor microenvironment, acts in an autocrine and paracrine manner through CXCR1/2 receptors on tumor, stromal, and immune cells, activating MAPK and PI3K pathways and promoting aggressive tumor behavior. EMT = Epithelial–mesenchymal transition; CAF =Cancer-Associated Fibroblasts; MDSC = Myeloid-Derived Suppressor Cells.

Table 1
Examples of genetic variants in *IL-8*, *CXCR1* and *CXCR2* genes.

Genetic variants	Reference SNP cluster ID	Biological effect	Cancer type	Ref
IL8				
+781C/T	rs2227306	Protective role	HCC	Zhang M, 2016 [12]
−251 T/A	rs4073	Cancer susceptibility	Breast cancer, Gastric cancer, NPC	Wang N, 2012 [13]
CXCR1				
+860C > G	rs2234671	Decreased DFS, CSS and OS	pCCA	Lurje I, 2022 [14]
-1566C/G	rs3138060	Cancer susceptibility	Breast cancer	Gallegos-Arreola MP, 2020 [15]
CXCR2				
+1208C/T	rs2227532	Cancer susceptibility	Breast cancer, Gastrointestinal cancers, Genitourinary cancers	Zhou J, 2021 [16]
+1208 TT	rs1126579	Cancer susceptibility	Breast cancer	Snoussi K, 2010 [17]

Legend. CSS = cancer-specific survival; DFS = disease-free survival; OS = overall survival, HCC = hepatocarcinoma, NPC = nasopharyngeal carcinoma, pCCA = perihilar cholangiocarcinoma.

regulation of IL-8 expression [4]. IL-8 expression is mostly regulated at the transcriptional and mRNA stability level, while protein turnover contributes less prominently. As a member of the ELR + chemokine family, IL-8 acts by binding and activating the selective CXCR1 (recognizing both IL-8 and GCP-2/CXCL6) and the more promiscuous CXCR2 (recognizing several ELR + chemokines, such as CXCL5 and CXCL7) receptors, within the context of partial functional redundancy across this chemokine family [5]. Despite redundancy, IL-8 retains a distinctive biological relevance, also due to its ability to engage both CXCR1 and CXCR2 and remains the most extensively investigated family member. Genetic variants have also been described in the *CXCR1* and *CXCR2* genes and potentially correlate with cancer prognosis. Some examples, reported in Table 1, include + 860C > G (rs2234671) and -1566C/G (rs3138060) for *CXCR1*, and + 1208 TT (rs1126579) and + 1208C/T (rs2227532) for *CXCR2*.

From a functional standpoint, IL-8 can contribute to a more aggressive biological and clinical tumor behaviour by acting at several levels. In cancer cells, it stimulates cell proliferation, epithelial-to-mesenchymal transition (EMT), migration and invasion, and promotes metastatic spread [6,7]. In the TME, IL-8 promotes angiogenesis and the recruitment of inflammatory cells, such as neutrophils, to induce the formation of tumor-promoting neutrophil extracellular traps (NET) [8,9]. Furthermore, IL-8 also enhances pro-tumoral properties of cancer-associated fibroblasts (CAF) [10] and immune-suppressive activities of myeloid derived suppressor cells (MDSC) [11].

In this review, we focus on the prognostic and/or predictive potential of IL-8 across different tumor types, potentially supporting its role as a tumor-agnostic biomarker (Table 2). We also discuss recent clinical evidence and mechanistic insights supporting the development of IL-8–targeted strategies to overcome resistance and improve treatment outcomes.

Interleukin-8 as a Prognostic/Predictive biomarker across different tumor types

Gastrointestinal cancers

Colorectal cancer (CRC)

Among GI cancers, the potential role of IL-8 has been most intensively investigated in CRC. We and others have demonstrated that the genetic/molecular background of CRC cells (BRAF mutations, PTEN loss, etc.) dictates their ability to produce IL-8, through modulation of specific transcription factors, such as NF-κB, AP-1, and CHOP [64,65]. IL-8 can affect several aspects of CRC cell behaviour, including stemness, plasticity, and metastatic ability [66,67]. From a clinical standpoint, several studies demonstrate a strong, statistically significant correlation between high IL-8 expression (particularly as measured in plasma or serum) and worse outcome, in terms of both overall survival (OS) and progression free survival (PFS), with a more than doubled risk of death for patients with high circulating levels of IL-8 detected in recent *meta*-analyses [65,68]; such prognostic effect appears to be independent of the type of systemic treatment applied (chemotherapy ± anti-angiogenic agents), thus suggesting a prognostic, rather than predictive, impact. Moreover, the IL-8–251 A/A polymorphism is related to a greater risk of tumor recurrence in resected, stage III CRC patients [69].

Esophago-gastric cancers. The prognostic/predictive relevance of IL-8 expression has been less studied in other GI tumors. In oesophageal cancer (both squamous cell carcinoma and adenocarcinoma), IL-8 and its receptor CXCR2 are overexpressed, as compared to healthy subjects or non-tumoral tissue, and have been reported to correlate with local invasion, nodal involvement, disease stage, and prognosis [70–72]. Selected IL-8 polymorphisms (−251 A/T, +781C/T, −353 A/T) appear to be involved in gastric cancer susceptibility [73]; one of these polymorphisms (−251 T > A) is also significantly associated with time to relapse (TTR; P = 0.003) and OS (P = 0.049, after adjusting for covariates), in localized gastric adenocarcinoma [74].

Pancreatic and liver cancers

In pancreatic cancer, IL-8 is upregulated downstream of TGFß-activated kinase 1 (TAK1) and the IL-8/CXCR2 axis promotes MMP-2 activity, thereby promoting invasion and metastasis [75]. Expression levels of IL-8 and CXCR2 (together with IL-6 and IL-10) are higher in cancer patients, as compared to healthy subjects or non-tumoral tissue, and correlate with lymph node metastases [76], therapeutic resistance, and poor survival [77,78]. Although IL-8 polymorphisms do not appear to confer increased risk of developing hepatocellular carcinoma (HCC) in a Chinese population [79], preclinical data suggest that IL-8 promotes

Table 2
Overview of key clinical trials on the prognostic role of IL-8.

First author, year	Study design	Study sample (N)	Histology	Stage	Type of treatment	Pts with IL-8 data	IL-8 detection	IL-8 cut-off	Results
Gastrointestinal cancers									
Suenaga M, 2020 [18]	Pooled analysis	125	CRC	IV	BEV vs TKI	125	Serum	15.1	**OS** HR 4.31 (95%CI 2.11–8.79, P < 0.001)
Marisi G, 2018 [19]	Prospective	376	CRC	IV	CT + BEV	58	Serum	145	**OS** HR 7.68 (95% CI: 2.59 –22.77, P = <0·001) **PFS** HR 7.39 (95% CI: 1.9–9.7, P = <0·001)
Tabernero J, 2015 [20]	Prospective	760	CRC	IV	TKI	611	Plasma	NA	**OS** HR 3.48 (95% CI: 2.39–5.06, P = <0·001) **PFS** HR 1.63 (95% CI: 1.22–2.18, P = <0·001)
Hamilton TD, 2014 [21]	Prospective	69	CRC	IV	Surgery	69	Serum	NA	**mOS** HR 4.96 (95% CI: 1.35–17.6, P = 0.014
Liu Y, 2013 [22]	Prospective	38	CRC	IV	CT + BEV	38	Plasma	NA (Range baseline 17.3–415.7)	**OS** HR 2.2 (95% CI: 1.06–4.4, P = 0.0304)
Spencer SKM, 2013 [23]	Retrospective	207	CRC	IV	CT vs CT + TKI	207	Serum	NA	High IL-8 levels associated with poor PFS and OS
Bruhn MA, 2013 [24]	Retrospective	471	CRC	IV	BEV	196	Tissue	NA (Range baseline 0.05–9.74)	**mPFS** (IL-8 ≤ 1.21) HR 0.51 (95% CI: 0.27–0.98, P = 46) **mPFS** (IL-8 ≥ 1.21) HR 0.76 (95% CI: 0.46–1.24, P = 46)
Genitourinary cancers									
Carril-Ajuria L, 2025 [25]	Prospective	353	RCC	IV	Nivolumab	353	Plasma	17.918 pg/mL	**OS** HR 2.11 (95% CI, 1.60–2.80).
Lin Y, 2025 [26]	Pooled analysis	2740	RCC + UC	IV	IO/TKI/BEV/ mTORinh	2740	Plasma	Different in each study	**OS** HR 1.86; 95% CI: 1.72–2.02 **PFS** HR 1.59; 95%CI: 1.25–2.03.
Powles T, 2021 [27]	Prospective	316	RCC	IV	Cabozantinib	NA	Plasma	4.601 pg/mL	**OS** HR 1.77 95% CI: 1.25–2.5 **PFS** HR 1.03 95%, CI: 0.76–1.4
Powles T, 2021 [27]	Prospective	305	RCC	IV	EVE	NA	Plasma	5.049 pg/mL	**OS** HR 1.67, 95% CI: 1.23–2.27. **PFS** HR 1.33, 95% CI: 1.01–1.76
Maynard JP, 2020 [28]	Retrospective	38	PCa	Localized	Not treated	38	Tissue	Continuous value	High IL-8 levels associated with **high grade PCa** (p = 0.005)
Yuen KC, 2020 (Imvigor210-Cohort 1) [29]	Prospective	119	mUC	IV	Atezo	88	Plasma	Median IL8 (NA)	**OS** HR 2.7, 95% CI: 1.48–4.87, p = 0.022
Yuen KC, 2020 (Imvigor210-Cohort 2) [29]	Prospective	310	mUC	IV	Atezo	241	Plasma	Median IL8 (NA)	**OS** HR = 1.84, 95% CI: 1.8, 2.26, P = 4.74E-05
Yuen KC, 2020 (Imvigor211-Cohort Atezo) [29]	Prospective	467	mUC	IV	Atezo	443	Plasma	Median IL8 (NA)	**OS** HR 1.84, 95% CI: 1.66–2.52, p = 7.19E-09
Yuen KC, 2020 (Imvigor211-Cohort CT) [29]	Prospective	464	mUC	IV	CT	425	Plasma	Median IL8 (NA)	**OS** HR 1.67, 95% CI: 1.38–2.03, p = 1.08E-07
Yuen KC, 2020 (IMmotion150) [29]	Prospective	103	mRCC	IV	Atezo	80	Plasma	Median IL8 (NA)	**OS** HR 2.55, 95% CI: 1.8–5.5, p = 0.017
Yuen KC, 2020 (IMmotion150) [29]	Prospective	101	mRCC	IV	ATEZO + BEV	82	Plasma	Median IL8 (NA)	**OS** HR 1.25, 95% CI 0.61–2.6, p = 0.535
Yuen KC, 2020 (IMmotion150) [29]	Prospective	101	mRCC	IV	sunitinib	79	Plasma	Median IL8 (NA)	**OS** HR 1.48, 95% CI: 0.69–3.2, p = 0.314

(*continued on next page*)

Table 2 (*continued*)

First author, year	Study design	Study sample (N)	Histology	Stage	Type of treatment	Pts with IL-8 data	IL-8 detection	IL-8 cut-off	Results
Harshman LC, 2020 [30]	Prospective	233	PCa	mHNPC	ADT+- docetaxel	233	Plasma	9.3 pg/ml	**mOS** HR 1.7 (95% CI: 1.2, 2.4, p = 0.007) **time to CRPC** HR 1.8 (95% CI: 1.3, 2.5, P < 0.001)
Schalper KA, 2020 [31]	Retrospective	392	RCC	IV	Nivolumab	392	Plasma	23 pg/mL	**OS** HR: 2,56 95% CI: 1,89–3,45 **PFS** HR: 1.36 95% CI: 1,07–1.772
Schalper KA, 2020 [31]	Retrospective	348	RCC	IV	EVE	348	Plasma	23 pg/mL	**OS** HR: 2,4; 95% CI: 1,78–3,2
Msaouel P, 2017 [32]	Retrospective	37	RCC (ccRCC + nccRCC)	IV	sunitinib versus EVE	37	Plasma	3.70 pg/mL sunitinib 5.18 pg/mL EVE	**OS** HR 3.55, 95% CI: 1.55–8.14 **PFS** HR 3.13 95% CI: 1.41–6.92
Bilen MA, 2015 [33]	Prospective	53	RCC (ccRCC + nccRCC)	IV	sunitinib	53	Plasma	22.32 pg/ mL	**OS** HR: 2.61, 95% CI: 1.03–6.58 **PFS** HR: 1.54, 95% CI: 0.87–2.72
Sharma J, 2014 [34]	Retrospective	122	PCa	mHNPC	ADT	122	Plasma	0.97 log10 pg/mL	**mOS** HR 1.9 (95% CI: 1.0, 3.5, P = 0.04) **time to CRPC** HR 1.4 (95% CI: 0.9, 2.2, p = 0.13)
Harmon CS, 2014 [35]	Prospective	33	RCC	IV	sunitinib	NA	Plasma	7 pg/mL	**OS** HR 1.11, 95% CI: 1.022–1.2
Harmon CS, 2014 [35]	Prospective	30	RCC	IV	IFN-α	NA	Plasma	9.5 pg/mL	**OS** HR 1.013 95% CI:0.969–1.06; **PFS** HR 1.018 95% CI:0.964–1.08
Lung cancer									
Rice SJ, 2021 (Cohort 1) [36]	Prospective	184	NSCLC	NA	IO/CT/ target therapy	184	Plasma	NA	**OS** HR 1.3 (95% CI 1.1–1.5, p = 0.004) **PFS** HR 1.2 (95% CI 1.00–1.4, p = 0.019)
Rice SJ, 2021 (Cohort 2) [36]	Prospective	51	SCLC	NA	IO/CT	51	Plasma	NA	**OS HR** 1.00 (95% CI 0.88–1.2, p = 0.806) **PFS** HR 1.1 (95% CI 0.92–1.2, p = 0.407)
Shi Y, 2021 [37]	Cohort study	59	NSCLC	III-IV	IO	59	Plasma	4.9 pg/ml	**PFS** HR 1.590 (95% CI:0.744–3.398, p = 0.231) **OS** HR 1.816 (95% CI: 0.699–4.718, p = 0.221)
Kauffmann-Guerrero, 2021 [38]	Prospective	29	NSCLC	IV	IO	29	Plasma	16.9 pg/ml	**PFS** (95% CI 2.71–5.29, P = 0.030)
Zhou J, 2021 [39]	Retrospective	156	All histologies (including SCLC)	IV	IO	42	Plasma	7 pg/ml	**PFS** HR 0.32 (95% CI 0.07–1.36, p = 0.087)
Sui X, 2021 [40]	Prospective	31	NSCLC	IIB – IIIB	CT/RT	31	Plasma	4.34 pg/ml	**PFS** HR 0.79 (95% CI 0.630–0.985, p = 0.036)
Gu L, 2021 [41]	Retrospective	232	NSCLC	I – IIIA	Surgery	232	Tissue	IHC > 3	**OS** HR 1.27 (95% CI 0.908–1.763p = 0.164) **DFS** HR 1.19 (95% CI 0.882–1.602, p = 0.256)
Schalper KA, 2020 (Cohort 1) [31]	Retrospective	135	Squamous NSCLC	IV	IO	108	Plasma	23 pg/ml	**OS** HR 1.84 (95% CI 1.19–2.83, p = 0.0051) **PFS** HR 1.28 (95% CI 0.81–2.00)
Schalper KA, 2020 (Cohort 2 – IO) [31]	Retrospective	292	Non-squamous NSCLC	IV	IO	255	Plasma	23 pg/ml	**OS** HR 1.90 (95% CI 1.42–2.53, p= <0.0001) **PFS** HR 1.60 (95% CI 1.19–2.15)
Schalper KA, 2020 (Cohort 2 – CT) [31]	Retrospective	290	Non-squamous NSCLC	IV	CT	253	Plasma	23 pg/ml	**OS** HR 2.98 (95% CI 2.12–3.98, P= <0.0001)

(*continued on next page*)

Table 2 (*continued*)

First author, year	Study design	Study sample (N)	Histology	Stage	Type of treatment	Pts with IL-8 data	IL-8 detection	IL-8 cut-off	Results
Hardy Werbin, 2019 (Cohort 2) [42]	Cohort study	37	SCLC	IV	IO	37	Plasma	13.82 pg/ml	**PFS** 6.9 *m* **OS** 17 m (P = 0.031)
Fidler MJ, 2017 (Cohort 1) [43]	Prospective	32	NSCLC	IIIB – IV	CT	32	Plasma	10 vs 90th percentile	**OS** HR 5.11 (95% CI 1.86–14.03, p = 0.002) **PFS** HR 4.94 (95% CI 1.77–13.76, p = 0.002)
Fidler MJ, 2017 (Cohort 2) [43]	Prospective	79	NSCLC	IIIB – IV	Target therapy	79	Plasma	10 vs 90th percentile	**OS** HR 1.18 (95% CI 0.92–1.51, p = 0.205) **PFS** HR 0.92 (95% CI 0.78–1.09, p = 0.339)
Cheng D, 2013 [44]	Prospective	71	All histologies, including SCLC	IV	CT	71	Pleural effusion	1693 pg/ml	**OS** HR 2.84 (95% CI 1.987–3.689, p = 0.001) **DFS** HR 2.38 (95% CI 1.245–3.555, p = 0.001)
Ryan BM, 2014 [45]	Retrospective	548	All histologies (including SCLC)	I – IV	NA	548	Plasma	75th percentile	**OS** HR 1.23 (95% CI 1.00–1.52, p = 0.047)
Seike M, 2007 [46]	Retrospective	80	NSCLC	I	Surgery	30	Tissue	6.4 pg/mg	**OS** HR 2.66 (95% CI 1.04–6.82, p = 0.03)
Orditura M, 2002 [47]	Prospective	60	NSCLC	III – IV	CT	60	Plasma	79.5 pg/ml	**OS** HR 2.89 (95% CI 1.40–5.97, p = 0.0025)
Melanoma									
Madsen CO,2025 [48]	Pooled analysis of prospective trials	47	Melanoma	IV	TIL-ACT	47	Plasma	Continuous value	Post Treatment IL-8 significantly higher among non-responders (p = 0.0016)
Levati L, 2024 [49]	Prospective	70	Melanoma	IV	BRAFi + MEKi	70	Plasma	4.32 pg/ml	**Mortality** HR 3.98 (95% CI 2.13–7.45, p= <0.0001) **Progression** HR 2.38 (95% CI 1.38–4.09, p= <0.002) IL-8 levels trend correlates with Best Response (p = 0.04) and Progression (p = 0.046).
Pedersen JG,2020 [50]	Prospective	16	Melanoma	IV	anti-PD1/anti-CTLA4	16	Plasma	Median value	No difference in **PFS**
Schalper KA, 2020 (Cohort 2) [31]	Retrospective	316	Melanoma	IV	Nivo	292	Plasma	23 pg/ml	**OS** HR 2.58 (95% CI 1.82–3.66, p= <0.0001)
Schalper KA, 2020 (Cohort 2) [31]	Retrospective	315	Melanoma	IV	Ipi	298	Plasma	23 pg/ml	**OS** HR 2.06 (95% CI 1.52–2.80, p= <0.0001)
Schalper KA, 2020 (Cohort 2) [31]	Retrospective	314	Melanoma	IV	Nivo + Ipi	297	Plasma	23 pg/ml	**OS** HR 3.06 (95% CI 2.13–4.41, p= <0.0001)
Lim S.Y, 2019 [51]	Prospective	58	Melanoma	IV	anti-PD1 + anti-CTLA4	58	Plasma	Median value	**OS** HR 5.14 (95% CI 1.11–23.84, p= <0.0197)
Jamal R, 2017 [52]	Prospective	30	Melanoma	IV	Ipilimumab + CBDCA-TXL	30	Plasma	76 pg/ml	**OS** HR 3.52 (95% CI 1.43–8.7, p= <0.0037)
Sanmamed MF, 2017 [53]	Prospective	29	Melanoma	IV	anti-PD1	29	Plasma	Concentration trend	IL-8 concentration trend correlates with Best Response (p = 0.001) and Progression (p = 0.004).
Sanmamed MF, 2017 [53]	Prospective	15	Melanoma	IV	anti-PD1 + anti-CTLA4	15	Plasma	Concentration trend	IL-8 concentration trend correlates with Best Response (p = 0.001).
Sanmamed MF, 2014 [54]	Prospective	27	Melanoma	IV	BRAF inhibitor	16	Plasma	60 pg/ml	**OS (IL-8 low)** HR 0.21 (95% CI 0.05–0.92, p = 0.038) IL-8 levels correlate with Best Response (p

(*continued on next page*)

Table 2 (*continued*)

First author, year	Study design	Study sample (N)	Histology	Stage	Type of treatment	Pts with IL-8 data	IL-8 detection	IL-8 cut-off	Results
									= 0.01) and Disease Progression (p = 0.05)
Sanmamed MF, 2014 [54]	Prospective	27	Melanoma	IV	Ipilimumab	8	Plasma	Concentration trend	IL-8 increase correlates with Disease Progression **OS** correlates inversely with IL-8 variations (p = 0.035)
Breast cancer									
Hutajulu SH, 2025 [55]	Prospective	168	Breast	I-IV	Naive	168	Plasma	6.77 pg/mL	**OS** HR 1.70 (95% CI 1.01–2.84, p = 0.044) **PFS** HR 1.42 (95% CI 0.71–2.84, p = 0.320) **DFS** HR 0.88 (95% CI 0.48–1.61, p = 0.690)
Gunnarsdottir FB, 2023 [56]	Prospective	156	Breast	IV	OT/CT/HER2-targeted/missing	136	Serum	NA	**OS** HR 1.63 (95% CI 1.33–1.98, p < 0.0001) **PFS** HR 1.44 (95% CI 1.18–1.76, p 0.00034)
Tiainen L, 2019 [57]	Secondary analysis of a prospective phase 2 trial	65	Breast	IV	Taxane + bevacizumab +/- ET	58	Plasma	9.4 pg/mL	**OS** HR 1.65 (95% CI 0.82–3.34, p = 0.159) **PFS** HR 1.32 (95% CI 0.58–3.00, p = 0.493)
Benoy IH, 2004 [58]	Prospective	77	Breast	I-IV	Naive	77	Serum	17.2 pg/mL	Overall postrelapse survival: significantly shorter in pts with IL-8 levels above cut-off value, p = 0.0045
Ovarian cancer									
Dobrzycka B, 2013 [59]	Prospective	118	EOC, all histologies	I-IV	cytoreductive surgery +/- platinum-based adjuvant CT	118	Serum	32.19 pg/mL	**OS** HR 2.32 (95%CI 1.53—3.64, p = 0.014) **DSF** HR = 0.94 (95%CI 0.86–3.58, p = 0.001)
Aune G, 2012 [60]	Retrospective	113	EOC, all histologies	I-IV	Surgery	113	Plasma	59 pg/ml	**Potential prognostic factors** HR 1.004 (95% CI 1.000–1.009, p = 0.029)
Merritt WM, 2008 [61]	Retrospective	102	EOC, all histologies	I-IV	cytoreductive surgery +/-paclitaxel- and platinum-based adjuvant CT	102	Tissue	IHC score: low (overall score 0–2) / high (3–4)	**Disease-specific survival:** HR 3.7 (95% CI 2.0–6.8, p = 0.001)
Head and Neck cancers									
Röhl L, 2023 [62]	Prospective	25	HNSCC	I-IV	IO	25	Serum Plasma	30 pg/ml 12 pg/ml	**OS** p = 0.106
Fujita Y, 2014 [63]	Prospective	50	OSCC	I-IV	Surgery	50	Serum Tissue	7.5 pg/ml IHC: positive expression > 5% of tumor and stromal cell	**DFS** longer in the Stage I/II OSCC patients with low serum IL-8 (p = 0.001)

Note. For all, but one (Sanmamed MF, 2014[54]), studies the hazard ratio (HR) for the comparison of patients with high IL-8 levels to those with low IL-8 levels (reference: 1).

Legend. CRC = colon rectal cancer; Atezo = Atezolizumab; ADT = androgen deprivation therapy; BEV: bevacizumab; CI = confidence interval; CRPC = castration resistance prostate cancer; CT = ChemoTherapy; HR= Hazard ratio; IL-8 = InterLeukin-8; IO = Immunotherapy; mOS = median overall survival; N = number; NA = Not Available; RCC = Renal Cell Carcinoma; UC = Urothelial Carcinoma; PCa= Prostate Cancer; mUC = metastatic Urothelial Carcinoma; mRCC = metastatic Renal Cell Carcinoma; ccRCC = clear cell Renal Cell Carcinoma; nccRCC = non-clear cell Renal Cell Carcinoma, NSCLC = Non-Small Cell Lung Cancer; OS = overall survival; PCa = prostate cancer; PFS = progression-free survival; pts = patients; RT = RadioTherapy; SCLC = Small Cell Lung Cancer. OSCC = Oral squamous cell carcinoma; HNSCC = head and neck squamous cell carcinoma; ET = endocrine therapy; IHC = immunohistochemistry.

an aggressive behaviour of malignant hepatocytes in terms of proliferation, migration and apoptosis. Indeed, in HCC, IL-8 is upregulated in cancer versus non-cancer tissue and correlates with tumor invasiveness and advanced stage [80]; moreover, high IL-8 levels, combined with ERK2 activation, are predictive of advanced stage, poor differentiation, and worse prognosis in terms of disease-free survival (DFS) and OS in resected HCC [81]. In intrahepatic cholangiocarcinoma, the IL-8—251 T/A or A/A polymorphisms are associated with shorter OS [82]; moreover, the + 860C > G polymorphism in the gene coding for the CXCL6 (GCP-2)/IL-8 receptor CXCR1 is an independent prognostic factor for DFS (p = 0.008), cancer specific survival (CSS; p = 0.001), and OS (p = 0.001) at multivariate analysis in resected perihilar cholangiocarcinoma [5,14].

Lung and thoracic cancers

Lung cancer (LC)

Numerous studies have suggested a potential correlation between IL-8 levels and worse prognosis in both small cell and non-small cell lung cancer (SCLC and NSCLC, respectively). As already discussed for CRC,

IL-8 production in LC depends on the tumor genetic background: IL-8 is transcriptionally upregulated by oncogenic KRAS in NSCLC [83,84], resulting in tumor-associated inflammation and neovascularization and correlating with adverse clinical factors (such as older age, smoking history, pleural and vascular invasion [83] and significantly reduced DFS and OS in resected patients [85]. Second, IL-8 promotes an immunosuppressive TME by recruiting MDSC and neutrophils, both of which inhibit cytotoxic T cell function and impair effective anti-tumor immune responses [5]. Additionally, IL-8 is associated with EMT, increased tumor cell plasticity, and angiogenesis, and modulates immune checkpoint expression, thereby indirectly and directly affecting the efficacy of immune checkpoint inhibitors (ICI) [5]. Third, IL-8 promotes stem-like traits, which are lost upon IL-8 knockdown, and suppresses drug-induced apoptosis in EGFR-mutant lung adenocarcinoma cells, resulting in reversible resistance to EGFR inhibitors in preclinical models and shorter PFS in gefitinib-treated patients [86]. Fourth, IL-8 produced by stromal cells, such as $CD248^{+}$ CAFs, may contribute to cisplatin resistance by activating the NF-κB signaling pathway and upregulating ABCB1 expression in mouse models *in vivo* [87]. Finally, IL-8 expression is deeply connected with chronic inflammation in NSCLC: in the context of chronic obstructive pulmonary disease, low circulating baseline levels of IL-8 and IL-2R result in longer PFS to ICI [39]; in cachectic NSCLC patients, muscle loss correlate with increased mRNA expression of pro-inflammatory cytokines, such as IL-8 and IL-6, which, in turn, cause muscular atrophy in preclinical models in vitro and are associated with reduced survival [88].

Overall, several lines of evidence support the use of IL-8 as a prognostic/predictive biomarker in NSCLC. Zou et al. conducted a systematic review and *meta*-analysis of 24 datasets from 14 pan-tumor studies (including NSCLC), showing that elevated IL-8 is consistently associated with lower objective response rates (ORR), reduced PFS, and less benefit from ICI treatment [2]; longitudinal changes in circulating IL-8 levels correlate with response to anti-PD-1 therapy [53];in particular, a decrease greater than 9.2% from baseline in circulating IL-8 within the first 2–3 weeks of treatment demonstrates high sensitivity and specificity in predicting objective response to ICI in both melanoma and NSCLC cohorts [53]. A recent systematic review and *meta*-analysis conducted by our group and encompassing 14 patient cohorts (accounting for over 2,600 subjects) treated with chemotherapy, immunotherapy, targeted therapy, and surgery, demonstrates that elevated serum IL-8 levels are significantly associated with poorer OS [pooled hazard ratio (HR): 1.75; 95% CI: 1.36–2.26) [89]. Although with a high degree of heterogeneity among studies, pooled analysis shows no significant difference in PFS between patients with high and low IL-8 levels, supporting a prognostic, rather than predictive, role of IL-8 in lung cancer [89]. Sensitivity analysis of OS data, however, shows a more prominent prognostic impact for circulating IL-8 in patients treated with chemotherapy or ICI, as compared with other treatments (encompassing targeted therapy and surgery) [89].

Malignant pleural mesothelioma (MPM) and thymoma

Although less established as a biomarker, IL-8 may play a role in other thoracic malignancies in addition to LC. In MPM, an autocrine circuitry involving Wnt, IL-1β, and IL-8 controls ABCB5 expression and tumor cell stemness, resulting in chemoresistance and worse time-to-progression (TTP) and OS on first-line chemotherapy [90]. In thymoma, IL-8 has been proposed as an auxiliary biomarker for diagnosis and monitoring, as its levels in naïve T cells are markedly elevated in patients with thymoma (as compared to those with other thymic tumors), decrease after surgical removal, and rise again when thymoma recurs [91].

Genitourinary cancers

Prostate cancer (PCa)

Preclinical evidence identifies IL-8 as a key orchestrator of immune suppression via polymorphonuclear (PMN)-MDSC recruitment in PCa models: castration leads to increased expression of IL-8, resulting in the recruitment of PMN-MDSCs and promotion of an immunosuppressive TME [92], PCa-derived exosomes transport IL-8, which impairs tumor-infiltrating $CD8^{+}$ T cells' activity by interfering with energy metabolism [93]. Such preclinical insights highlight the IL-8/CXCR2 axis as a biomarker of immune resistance and possibly a promising therapeutic target in PCa. From a clinical point of view, elevated circulating IL-8 levels at androgen deprivation therapy (ADT) initiation have been consistently associated with a shorter time to castration resistance and reduced OS in advanced PCa [34]. These findings were confirmed in the CHAARTED trial, enrolling patients with metastatic hormone-naïve PCa and comparing ADT alone versus ADT in combination with docetaxel chemotherapy: elevated circulating IL-8 correlated with worse survival and shorter time to castration-resistance, irrespective of docetaxel administration, metastatic burden, and metachronous versus *de novo* metastatic presentation [30]. IL-8 expression in the TME of PCa patients correlates with aggressive disease and androgen receptor loss in metastatic disease, correlating with more aggressive tumor phenotypes and poorer clinical outcomes [28].

Urothelial and Renal cell carcinoma

In metastatic urothelial carcinoma (mUC) and metastatic renal cell carcinoma (mRCC), elevated baseline IL-8 levels in plasma, peripheral blood mononuclear cells, and tumor tissue are significantly associated with worse OS and reduced efficacy of atezolizumab across three pivotal clinical trials (IMvigor210, IMvigor211, IMmotion150; n = 1,445 patients). Moreover, a significant association between high IL-8 levels and OS was evident for chemotherapy (mUC), but not for anti-angiogenic agents containing (mRCC) treatment arms, while dynamic changes in on-treatment IL-8 levels were significantly associated with OS in mUC receiving ICI [29]. Elevated baseline circulating IL-8 has also been associated with worse outcomes in a real-world study assessing the activity of nivolumab in pretreated advanced RCC [25]. Collectively these data support high circulating IL-8 as a biomarker of poor prognosis and resistance to ICI in mUC and mRCC [29]. In the ABACUS trial comparing neoadjuvant ICI with or without chemotherapy in muscle-invasive bladder cancer, high pre-treatment IL-8 signature predicted better response to neoadjuvant ICI as compared with ICI alone, supporting the hypothesis that chemotherapy may mitigate IL-8 driven immune resistance [94]. A recent *meta*-analysis encompassing both mUC and mRCC tumor types demonstrated a significant correlation between circulating high IL-8 levels and OS and PFS in patients with both urologic malignancies [26]. Notably, subgroup analyses revealed that this negative prognostic was more pronounced in patients treated with ICI than in those receiving tyrosine kinase inhibitors (TKIs). Consistently, analysis of TCGA RNA seq data confirmed that high tumor CXCL8 expression correlated with reduced OS and DFS in patients with urologic malignancies [26]. Our recently published *meta*-analysis, involving over 1,700 RCC patients in six clinical trials, confirmed the independent prognostic value of circulating IL-8. Elevated IL-8 levels were significantly associated with reduced OS ([HR] 1.85; 95% [CI] 1.21–2.84; p = 0.001) and PFS (HR 1.27; 95% CI 1.01–1.59; p = 0.037) [95]. Subgroup analyses revealed that such negative prognostic impact was particularly pronounced in patients treated with ICI or mTOR inhibitors (HR 2.57 and HR 2.01, respectively), while the association was weaker or absent in those receiving TKIs (HR 1.47) [95]. These findings support IL-8 as a robust prognostic biomarker in RCC and suggest its potential utility for guiding treatment selection; publicly available tissue-based IL-8 transcriptomic data show a qualitatively similar trend towards association with poorer survival outcomes in resected clear-cell and non-clear cell RCC, again suggesting that the prognostic/predictive impact of IL-8 is independent from either the source of assessment or the histological subtype [95].

Testicular and penile cancer

Although data remain limited in testicular and penile cancers, preliminary studies suggest that intratumoral IL-8 is upregulated alongside other pathways involved in cell proliferation [96]. However, further research is needed on these rarer genitourinary tumor types to draw definitive conclusions regarding the prognostic and potentially predictive role of IL-8.

Melanoma

IL-8 is overexpressed in melanoma compared to normal melanocytes and appears to be positively regulated by hypoxia-dependent transcriptional mechanisms [97]; IL-8 is also secreted by endothelial cells, which predominantly secrete a specific IL-8 isoform, IL-8_{77}, that has twice the chemotactic potency of the IL-8_{72} isoform secreted by melanoma cells [98]. As for CRC, BRAF mutations are a major driver of IL-8 transcription in melanoma [99,100]. CXCR1 and CXCR2 have also been found to be constitutively expressed and upregulated under hypoxic conditions in melanoma [101–103], with higher levels observed in more aggressive cell lines [104]. IL-8 and CXCR2 expression levels exhibit a linear correlation and are associated with both Clark level and tumor thickness (Breslow $>$ 0.75 mm); moreover, lower levels of the long non-coding RNA Lnc-PKNOX1-1, which negatively regulates IL-8 expression, are found in melanoma patients with greater tumor depth, and higher IL-8 mRNA levels are found in metastatic lesions, as compared to primary tumors [105,106] and may contribute to maintaining melanoma cell stemness [107]. From a clinical perspective, serum IL-8 levels have been associated with adverse outcomes in patients receiving ICI. In a large cohort derived from pivotal phase III clinical trials involving melanoma, NSCLC, and RCC, elevated serum IL-8 concentrations were significantly correlated with reduced OS across tumor histologies, with the most pronounced effect observed in melanoma patients treated with the combination of nivolumab and ipilimumab [31]. Such negative prognostic association was independent of PD-L1 expression and tumor mutational burden (TMB). Furthermore, higher serum IL-8 levels were linked to increased peripheral monocyte and neutrophil counts, while intratumoral IL-8 expression was associated with enhanced monocyte and neutrophil infiltration and diminished IFN-γ- and T-cell–related transcript signatures, indicating a more immunosuppressive TME [31]. Consistently, a *meta*-analysis by Zou et al. confirmed the unfavourable prognostic impact of elevated IL-8 levels across multiple tumor types and ICI regimens [2]. High circulating IL-8 levels has also been shown to predict poorer outcomes in patients receiving adoptive cell therapy and changes in IL-8 levels post-treatment also correlate with response or failure to such treatment [48]. In terms of treatment monitoring, several studies have demonstrated a correlation between IL and 8 levels and therapeutic response, with IL-8 levels declining in responders to ICI and rising in those with progressive disease (possibly allowing to distinguish true progression from pseudo-progression) [53,54,108]. Levati et al. corroborated these findings, showing that IL-8 plasma levels dropped after two months of targeted therapy and that elevated baseline IL-8 levels were associated with shorter PFS and OS [49]. Taken together, this body of evidence highlights a central role of IL-8 in melanoma growth, progression, migration, stemness, and its strong negative prognostic value, independent of treatment modality. IL-8 is also emerging as a promising biomarker for treatment monitoring, particularly in the context of immunotherapy, where it may help interpret ambiguous clinical responses.

Breast, head and Neck, and ovarian cancer

Breast cancer (BC)

In BC, IL-8 is secreted by both tumor cells and components of the TME [109,110]. Preclinical studies show that abnormal IL-8 expression increases BC cell invasiveness and metastatic potential [111] and sustains stem cell survival [112]. Moreover, silencing IL-8 via siRNA in preclinical models of ER-negative BC enhances docetaxel efficacy by inducing cell cycle arrest and reducing proliferation [113]; inhibiting endogenous IL-8 also sensitizes multidrug-resistant MCF-7 cells to doxorubicin [114]. In triple-negative BC (TNBC), high IL-8 expression cells are associated with paclitaxel sensitivity but doxorubicin resistance, via an NF-κB feedback loop promoting survival, Akt/mTOR signaling, and autophagy suppression [115]. Moreover, a large bioinformatics analysis confirmed that IL-8 promotes an immunosuppressive TME, positively correlating with M0 macrophages and activated mast cells, and negatively correlating with CD8 + T cells and resting mast cells; IL-8 expression also correlates with markers of immune escape, including EMT, checkpoint gene expression, high TMB, and poor immunophenoscore [116]. In luminal A BC, elevated IL-8 correlates with reduced tumor-infiltrating lymphocytes, again suggesting an immunosuppressive effect [117]. Clinically, IL-8 expression is higher in aggressive, triple-negative and HER2-enriched tumors, as compared to estrogen receptor (ER)-positive cases [118]; circulating IL-8 also tends to be elevated in these subtypes, where its prognostic value seems greater [119]. High circulating IL-8 levels correlate with more advanced disease [120,121] and independently predict OS and, albeit less consistently, DFS or PFS [55,56]. Of note, IL-8 expression within the TME also appears to be linked to shorter relapse-free survival (RFS)/PFS [122,123], possibly through an inverse correlation with ER expression [123] and a positive association with MMP-9 [124]; in other studies low IL-8 expression by IHC was linked to increased metastasis and recurrence, while high IL-8 was more common in patients who died during follow-up [125]. High IL-8 mRNA levels in tissues of BC patients are also linked to aggressive, poorly differentiated features and associate with worse RFS and OS [126,127]. In TNBC, IL-8 gene signatures predict poor prognosis, while B-cell signatures predict better outcomes; patients with low IL-8 and high B-cell expression exhibit better 5-year EFS, even without systemic therapy [128]. In the neoadjuvant TNBC setting, correlation of circulating IL-8 levels at baseline and at the time of surgery were inconsistently associated with pathologic complete response [129,130]; however, CXCR1/2 expression was an independent prognostic factor for DFS [130]. Persistently high or increasing IL-8 levels during treatment correlate with treatment resistance and worse outcomes [57,131–133]. Overall, preliminary evidence suggests IL-8 as a prognostic/predictive biomarker in BC, albeit with some inconsistencies, related to heterogeneity in patient populations, treatment regimens, and assay methodologies, and with a possible discrepance between the prognosis-modulating impact of circulating and tissue IL-8 levels.

Head and neck squamous cell carcinoma (HNSCC)

Preclinical evidence suggests a pivotal role for IL-8 in HNSCC progression. HNSCC cell lines show higher IL-8 mRNA and protein levels, as compared to normal epithelial cells [134]. Through CXCR1/2 activation, IL-8 enhances proliferation and clonogenicity, invasion, metastasis, chemoresistance, and EMT [135]. IL-8 is also secreted by TME components [136], recruits tumor-promoting neutrophils [136], inhibits FOXP3 expression [137], promotes monocyte differentiation into $CD206^{+}$ TAMs [138], and activates STAT3 in fibroblasts. This leads to extracellular matrix degradation and increased tumor invasiveness [10]. IL-8 is overexpressed in HNSCC tumor tissues versus healthy mucosa [139] and correlates with more advanced disease [134]. Circulating IL-8 levels are usually higher in HNSCC patients than in healthy controls [140], including those with dysplasia [141] or in remission [142], although with some inconsistencies [143,144]. Notably, HPV-negative HNSCC cell lines secrete more IL-8 and an HPV + status correlates with lower IL-8 levels [139]. Serum IL-8 is variably associated with HNSCC outcomes: while some studies found no correlation [140,145], a biomarker analysis of 498 stage III-IV HNSCC patients treated with chemo/radiotherapy reported that high baseline IL-8 independently predicted worse OS (HR 1.55, $p = 0.007$) [146]. Longitudinal data indicated that relapsing patients had higher IL-8 circulating levels 7

weeks after treatment start [147], while low serum IL-8 correlated with longer DFS in stage I/II patients, but not in later-stage oral SCC [63], tumor IL-8 expression and M2 CD163 + macrophage infiltration at the invasive front correlated with elevated serum IL-8 and worse DFS in full cohort, suggesting that serum IL-8 may reflect TME composition [63]. High IL-8 expression within the HNSCC TME associates with poor prognosis in oral SCC [138], while elevated IL-8 levels by RT-PCR predicted a 4.1-fold increased risk of local recurrence in stage I-IV HNSCC patients treated with radiotherapy or chemoradiotherapy [148]. Notably, Jing et al. reported better OS with low IL-8 in HPV+, but not in HPV-, patients [149]. Transcriptomic analyses also link high IL-8 mRNA with worse OS [150]. Dynamic IL-8 changes in HNSCC show a non-significant trend towards the association of increased circulating IL-8 levels during therapy and suboptimal treatment response [151]. During ICI therapy increasing or persistently elevated IL-8 levels predict lack of response, disease progression, and worse OS [62,152]. Overall, in HNSCC circulating IL-8 appears to reflect tumor burden and immune microenvironment composition and function, and may predict response, especially in patients treated with immunotherapy.

Epithelial ovarian cancer (EOC)

IL-8 is a key mediator in EOC progression, promoting cell survival and proliferation, migration and metastasis, EMT, angiogenesis, cancer stem cell–like traits, and immune evasion [153]. Several mechanistic studies, highlight the therapeutic potential of the inhibition of the IL-8-CXCR1/2 axis in EOC models, where it enhances cisplatin sensitivity and reverses resistance [154], and reduces tumor growth, survival, migration, microvascular density, and cell proliferation [155]. Moreover, IL-8/CXCR2 signaling blockade reduces M2 macrophage polarization, thereby decreasing both tumor growth and M2 macrophage infiltration [156].

From a clinical standpoint, evidence suggests that elevated IL-8 levels – both circulating and in tumor tissue – are associated with poor prognosis in EOC, although with some inconsistencies [157]. High baseline circulating IL-8 has been linked to lower 5-year OS in surgical patients [60], and with poorer OS and DFS in cohorts treated with platinum-based adjuvant chemotherapy [61], or anti-angiogenic treatment [158]; similarly, a prospective study of 24 patients across stages I–IV found that high tissue IL-8 expression correlated with poor survival [159]. Dynamic changes in IL-8 levels show potential as a biomarker for predicting chemotherapy response [160,161], with decreasing levels correlating with response and increasing levels correlating with drug-resistance [162,163]. Overall, IL-8 acts as a pleiotropic mediator in EOC and its association with aggressive tumor behaviour, poor prognosis, and chemoresistance highlights its potential as a biomarker and a therapeutic target.

Circulating versus tissue IL-8 levels

Circulating IL-8 levels may reflect overall tumor burden and/or a tumor-induced systemic inflammatory response. Sanmamed et al. showed that circulating IL-8 levels correlate with tumor burden in multiple histotypes [53,54]. Due to its short half-life and renal clearance, circulating IL-8 levels accurately reflect even small variations in tumor burden [164], making its standardized, minimally-invasive, detection an ideal tool to dynamically monitor treatment response, particularly to immunotherapy [31,165,166]. Selective variations in serum IL-8, not associated with variations in other inflammatory biomarkers, in NSCLC patients responding or not to immunotherapy are suggestive of increasing tumor burden upon treatment failure [53]. On the other hand, serum IL-8 levels may represent a general inflammatory biomarker. In healthy conditions *IL-8* gene expression is repressed, and serum IL-8 increases in response to several inflammatory processes not related to cancer [167,168], such as immunological, cardiovascular and neurological diseases, dermatitis, infections, autoimmune responses and environmental stress [164,169–172]. As a pro-inflammatory mediator, IL-8 is also involved in inflammaging, a persistent low-grade systemic inflammatory condition occurring during aging. Persistent DNA damage and immunosenescence in aging activate transcription factors like NF-κB and C/EBPβ, upregulating IL-8 along with other inflammatory cytokines such as IL-6 and IL-1α. Elderly individuals show overproduction of IL-8 by monocytes, as compared to younger people, fueling systemic inflammation [173–175]. Elevated IL-8 levels, in turn, promote neutrophil chemotaxis, oxidative stress, and tissue damage, exacerbating inflammaging and linking it to age-related diseases including neurodegeneration and cancer [176]; indeed, inflammaging may also serve as a prognostic tool in cancer patients [177]. While the source of IL-8 production (tumor versus inflammatory cells) may help dissect whether its variations are rather the result or the cause of tumor response or progression in cancer patients, it is very difficult to separate these two deeply intertwined aspects. Most likely, IL-8 is part of a self-amplifying loop linking high tumor burden to a pro-tumoral inflammatory state, angiogenesis, neutrophil infiltration, immune suppression, and metastasis, in turn worsening tumor burden.

In the prognostic/predictive analyses described here, there is a general concordance between serum and tissue IL-8 levels in different tumor histotypes. For example, recent evidence shows that early and sustained variations in circulating IL-8 levels reflect tissue variations, predicting response to cemiplimab in cutaneous squamous cell carcinoma [178]. However, discrepancies can be observed in the prognostic/predictive impact of circulating versus tissue IL-8 expression, particularly in CRC [65]. Methodological biases could potentially explain the relative discrepancies between different sources of IL-8 detection (for example, imbalance in tissue versus serum samples – 1761 versus 82 gastric cancer patients[179]). Methodological biases notwithstanding, some observations in CRC raise the interesting biological hypothesis that local production of IL-8 may actually result in immune activation and control of tumor growth. For example, Li et al. identified a high-ImmuneScore population highly expressing IL-8 mRNA, which correlated with better CRC survival; IL-8 was associated with dendritic cell (DC) activation markers (CD80, CD83, CD86), suggesting an active antitumor immune response; CXCR2 blockade resulted in reduced local DC activation and decreased expression of IFN-γ or granzyme B by $CD8^+$ T cells, thereby fostering CRC progression *in vivo* [180]. Consistent with this hypothesis, IL-8 expression in tumor-infiltrating mononuclear cells correlates with earlier disease stage ($P < 0.001$) and improved ($P < 0.001$) relapse-free survival [181]. In a series of 168 CRC specimens, PTEN-loss in cancer cells [65], a prognostically unfavorable molecular trait [182], significantly correlated with the lack of tumor-infiltrating $IL\text{-}8^+$ mononuclear cells.

Analysis of the potential prognostic/predictive value of IL-8 receptors (CXCR1/CXCR2) is even more complex, due to the specific relationships between receptor expression and IL-8 activity and to the fact that circulating CXCR1/2 levels may not accurately reflect the signal transduction mechanisms occurring in tumor tissue; in addition, CXCR1/2 are pleiotropic receptors with multiple ligands, whose activity may reflect not only stimulation by IL-8. As a result, at a difference with IL-8 expression, which linearly increases in serum and tissue with tumor grading, CXCR1/2 levels show different trends in serum and tissue, regardless of the stage of disease progression, in an EOC dataset [183].

Discussion

Several studies reviewed herein have evaluated the prognostic role of IL-8 in various types of cancer. High IL-8 expression has generally been associated with poor prognosis in GI, thoracic, and GU malignancies, as well as in melanoma (Fig. 2).

In particular, IL-8 has emerged as a useful predictive biomarker for identifying patients who are more likely to benefit from ICI, as lower plasma levels of this chemokine are associated with improved immunotherapy responses and enhanced clinical outcomes [5]. While these findings, supported by well-established mechanistic explanations

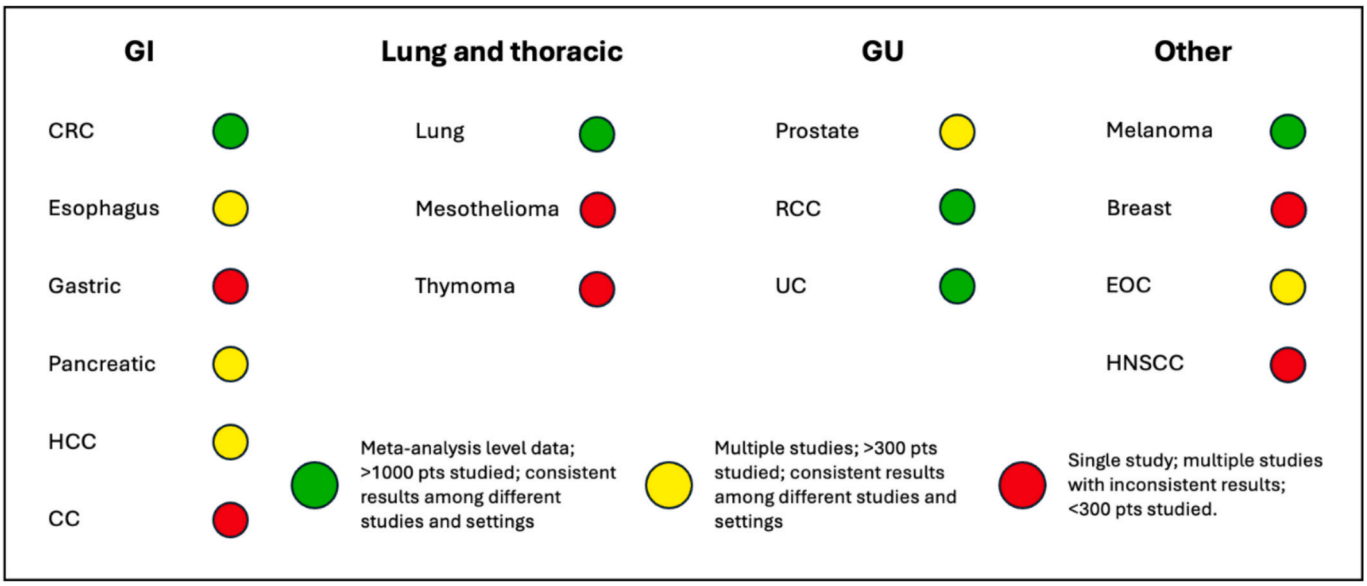

Fig. 2. Clinical relevance of IL-8 across solid tumors. Schematic overview of the strength and consistency of the available clinical evidence on the prognostic and/or predictive role of IL-8 across different solid tumor types. Overall, elevated circulating and/or intratumoral IL-8 is most consistently associated with poor clinical outcome, higher tumor burden, and treatment resistance, although the level of evidence varies across tumor settings. Legend. GI = gastrointestinal; GU = genito-urinary; CRC = colorectal cancer; HCC = hepatocellular carcinoma; CC = cholangiocarcinoma; RCC = renal cell carcinoma; UC = urothelial carcinoma; EOC = epithelial ovarian cancer; HNSCC = head and neck squamous cell carcinoma.

linking IL-8 production to an immunosuppressive TME and JAK2/STAT3-mediated PD1 expression and T-cell exhaustion, support IL-8 as a prognostic/predictive biomarker across multiple cancer types, heterogeneity of the studies analysed, in terms of patient populations, source (circulating versus tissue), quantification methods, and IL-8 cut-off values, limits the consistency of the conclusions and highlights the need for prospective and standardized investigations. Of note, IL-8 and its receptors CXCR1/2 have emerged as promising therapeutic targets in oncology, with strategies ranging from neutralizing antibodies to small-molecule antagonists and RNA-based approaches (Fig. 3). Preclinical models confirm this rationale: in OSCC, IL-8 blockade reduces invasion, migration, and cisplatin resistance by suppressing NF-κB–driven EMT [135], while in EOC models, IL-8 neutralization/knockdown limits invasion and reverses cisplatin resistance [154,184,185]. CXCR1/2 inhibition has shown comparable promise, with agents such as SX-682 and navarixin reprogramming the TME, reducing MDSC infiltration, and enhancing PD-1/PD-L1 blockade in glioma, lung, and pancreatic models [186]. Dual targeting approaches, including combined CXCR1/2 and

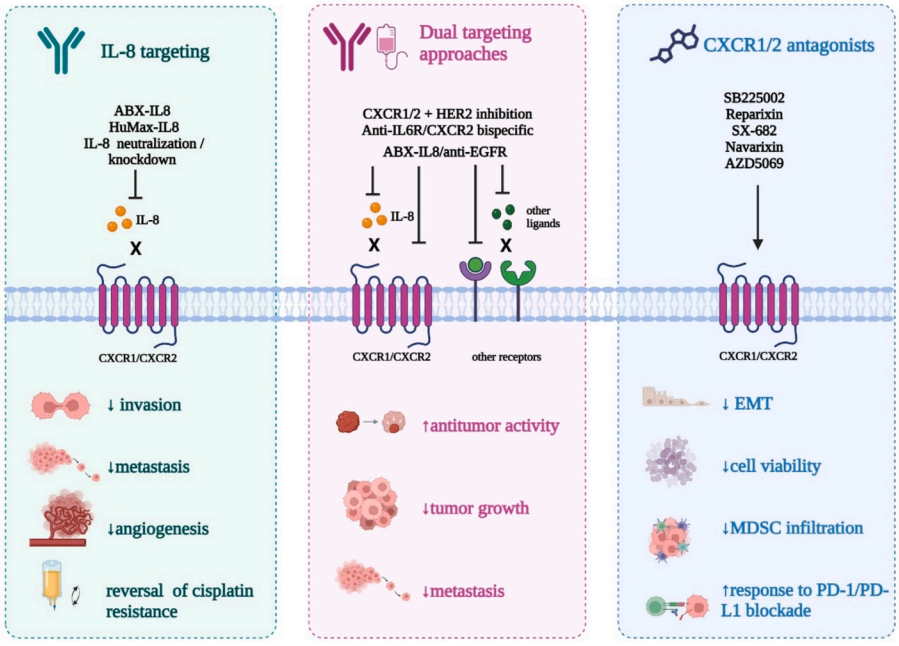

Fig. 3. Therapeutic intervention strategies. Targeting the IL-8/CXCR1/2 axis through ligand neutralization (e.g., anti–IL-8 antibodies) or CXCR1/2 antagonists (e.g., SB225002, reparixin, SX-682, navarixin, AZD5069) inhibits downstream signaling, reducing EMT, tumor cell viability, and immunosuppressive cell infiltration, while enhancing therapeutic responses. Combination strategies further improve antitumor efficacy. Legend. IL-8 = interleukin 8; EMT = Epithelial–mesenchymal transition; MDSC = Myeloid-Derived Suppressor Cells.

HER2 inhibition [187] or bispecific antibodies against IL-6R and CXCR2 [188], further support the axis as a potential target to reverse resistance and metastasis. In TNBC, CXCR2 antagonists like SB225002 reduce cell viability, EMT, and metastasis both in vitro and *in vivo*, outperforming reparixin in suppressing 4 T1 cell colonization in murine models [189,190]. Interestingly, in preclinical CRC models the CXCR2 antagonist SB225002 reduces cell viability via apoptotic and non-apoptotic mechanisms in CRC cells and normal fibroblasts, respectively, in a CXCR2-indepndent fashion [191]. The anti-IL-8 antibody (ABX-IL8) reduced metastasis, angiogenesis, and enhanced apoptosis in melanoma mouse models, while in vitro it inhibited capillary formation and MMP2 activity [192]; its combination with the anti-EGFR antibody (ABXEGFR) further improved survival, decreased tumor growth and metastasis in SCID mice, and reduced MMP activity in breast carcinoma cells (MDA-231) [5,193]. Clinical translation is ongoing. HuMax-IL8 (BMS-986253), a human monoclonal antibody, has demonstrated safety and preliminary activity in phase I trials and is now being tested in combination with nivolumab in NSCLC, HCC, and prostate cancer [3]. Multiple CXCR2 antagonists, including AZD5069, Navarixin, and SX-682, are under clinical evaluation, often in combination with immunotherapy [3,194]. In PCa, AZD5069 combined with enzalutamide showed a favorable safety profile and clinical activity in mCRPC patients resistant to AR pathway inhibitors [195]. Similarly, reparixin plus paclitaxel was tested in HER2-negative metastatic breast cancer, achieving an ORR of 29.6% with acceptable tolerability [196] (Fig. 3).

Despite this robust preclinical rationale and promising signals from early-phase studies, it must be acknowledged that the clinical translation of IL-8/CXCR1-2 pathway inhibition has so far yielded limited benefit for cancer patients, and few agents targeting this axis have advanced beyond Phase I trials. Available Phase II data are largely negative: the combination of the CXCR2 antagonist navarixin with pembrolizumab failed to demonstrate meaningful clinical activity in a randomised Phase II trial across multiple advanced solid cancer previously treated [197]; the CXCR1/2 inhibitor reparixin combined with paclitaxel did not meet its primary endpoint in untreated TNBC [198]; the addition of anti-IL-8 monoclonal antibody BMS-986253 to ipilimumab and nivolumab failed to improve ORR and PFS over placebo in patients with advanced melanoma resistant to PD-(L)1 blockade [199]. It is also important to consider that preclinical models, largely based on syngeneic or xenograft systems, may fail to fully recapitulate the complexity of the human tumor microenvironment or the heterogeneity of clinical disease. The study of biological IL-8 functions in preclinical models *in vivo* is hampered by the fact that rodents lack a homologue of human *IL-8*; instead, mice have the functional homologues *CXCL1/KC*, *CXCL2/MIP-2* and *CXCL5-6/LIX*, belonging to the same clusters of cytokines involved in neutrophils migration [200]). Organization and function of the mouse homologues of human IL-8 also sheds light how compensatory mechanisms and built-in redundancy within TME are likely to limit the impact of IL-8/CXCR1/2 blockade as a single immunomodulatory intervention, suggesting that more effective strategies will require rational combination approaches capable of broader TME reprogramming. Indeed, as highlighted above, CXCR1 binds IL-8 plus CXCL6/7, while CXCR2 binds a broader set (CXCL1-3, CXCL5-8), allowing compensatory signaling when one is inhibited [201,202]. Moreover, CXCR2 compensates for CXCR1 blockade (e.g., repertaxin or reparixin, as both drive angiogenesis, neutrophil recruitment, and MDSC infiltration; dual inhibition is often needed but still incomplete due to low-affinity agonists [139]. In response to monotherapies with anti-IL-8 monoclonal antibodies or CXCR2 inhibitors, tumors upregulate alternative ELR + CXCL ligands via NF-κB, sustaining protumoral inflammation, thus requiring pan-CXCR1/2 or sequential combo strategies, as single agents would likely fail to interfere with such a robust chemokine network [203]. Furthermore, patient selection has been largely unrefined in Phase II trials. Given the well-documented prognostic role of baseline IL-8 levels, and its emerging potential as a predictive biomarker, enrichment strategies based on circulating or tumor-associated IL-8 expression may be necessary to identify patients most likely to benefit from pathway inhibition. Overall, these considerations underscore the need for biomarker-driven clinical trial designs, as well as a more refined understanding of the tumor contexts in which IL-8 signalling represents a functional dependency, before the therapeutic potential of this axis can be fully realised in the clinic.

Conclusion

IL-8 represents a promising predictive and prognostic biomarker in solid tumors, particularly in CRC, NSCLC, RCC, and melanoma, where IL-8 measurement has the potential to guide personalized therapeutic decisions and open new targeted therapeutic avenues; well designed, prospective studies are required to promote full integration of IL-8 (and possibly CXCR1/2) measurement into standard oncology practice in wider array of solid malignancies.

Fundings

This review received no funding.

This review did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Ilaria Mariangela Scaglione: Conceptualization, Methodology, Writing – original draft. **Chiara Bazzichetto:** Conceptualization, Methodology, Writing – original draft. **Michele Borghesani:** Data curation, Writing – original draft. **Francesca Zacchi:** Data curation, Writing – original draft. **Serena Eccher:** Data curation, Writing – original draft. **Marco Sposito:** Data curation, Writing – original draft. **Jessica Insolda:** Data curation, Writing – original draft. **Elena Giontella:** Data curation, Writing – original draft. **Elena Trevisani:** Data curation, Writing – original draft. **Alice Avancini:** Data curation, Writing – original draft. **Daniela Tregnago:** Data curation, Writing – original draft. **Sara Cingarlini:** Data curation, Writing – original draft. **Sara Pilotto:** Data curation, Writing – original draft. **Fabiana Conciatori:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Lorenzo Belluomini:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Michele Milella:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Sara Pilotto received honoraria or speakers' fees from AstraZeneca, Eli Lilly, Bristol-Myers Squibb, MSD, Takeda, Amgen, Novartis, Roche, Daiichi-Sankyo, Pierre-Fabre, Boehringer Ingelheim and J&J, outside the submitted manuscript. Lorenzo Belluomini received speakers' fees from AstraZeneca, Merck Sharp & Dohme, Takeda, Novartis, Bristol-Myers Squibb, MSD and Roche, and travel fees from Takeda, Servier, J&J, outside the submitted manuscript. Michele Milella received honoraria or speakers' fees from AstraZeneca, MSD Oncology, Ipsen, Hippocrates Research, Viatris, Servier. MM received consulting or advisory role from AstraZeneca, MSD Oncology, Janssen Oncology. MM is involved in steering committee promoted by Novartis, OncoSil and received Research funding from Roche].

Acknowledgments

SP is supported by the Associazione Italiana per la Ricerca sul Cancro (AIRC, Next Gen Clinician Scientist 2023 n° 30204). LB is supported by grants from Associazione Pietro Casagrande ONLUS. MM is supported by PRIN 2022: Understanding and dissecting the role of Tumor

microEnvironment of Lung Adenocarcinoma in the era of precision medicine (TELUAD). MM is supported by FIMP: PANCREATIC TUMOR GENOME: CLINICAL APPLICATION OF THE RESULTS". MM is supported by HEAL ITALIA: PNRR_HEAL_ITALIA_DIMI_S8 – PNRR. MM is supported by PNRR_INNOVA_DIMI "Progetto PNC-E3-2022-23683266-PNC-HLS-DA, HUB LIFE SCIENCE - DIAGNOSTICA AVANZATA. MM Is supported by the European Union - Next Generation EU - NRRP M6C2 - Investment 2.1 Enhancement and strengthening of biomedical research in the NHS, Project PNRR-MAD-2022-12375670. MM Is supported by European Union - Next Generation EU - "Addressing liver fibrosis prevention and treatment: an unbiased query on the hepatic microenvironment with a perspective targeting of the profibrotic kinase HIPK2" - PNRR -MAD-2022-12375670

References

[1] Baggiolini M, Walz A, Kunkel SL. Neutrophil-activating peptide-1/interleukin 8, a novel cytokine that activates neutrophils. J Clin Invest 1989;84:1045–9. https://doi.org/10.1172/jci114265.

[2] Zou D, Song A, Yong W. Prognostic role of IL-8 in cancer patients treated with immune checkpoint inhibitors: a system review and meta-analysis. Front Oncol 2023;13:1176574. https://doi.org/10.3389/fonc.2023.1176574.

[3] Fousek K, Horn LA, Palena C. Interleukin-8: a chemokine at the intersection of cancer plasticity, angiogenesis, and immune suppression. Pharmacol Ther 2021; 219:107692. https://doi.org/10.1016/j.pharmthera.2020.107692.

[4] Dakal TC, et al. Predicting the functional consequences of non-synonymous single nucleotide polymorphisms in IL8 gene. Sci Rep 2017;7:6525. https://doi.org/10.1038/s41598-017-06575-4.

[5] Meier C, Brieger A. The role of IL-8 in cancer development and its impact on immunotherapy resistance. Eur J Cancer 2025;218:115267. https://doi.org/10.1016/j.ejca.2025.115267.

[6] Ning Y, et al. Interleukin-8 is associated with proliferation, migration, angiogenesis and chemosensitivity in vitro and in vivo in colon cancer cell line models. Int J Cancer 2011;128:2038–49. https://doi.org/10.1002/ijc.25562.

[7] Palena C, Hamilton DH, Fernando RI. Influence of IL-8 on the epithelial-mesenchymal transition and the tumor microenvironment. Future Oncol 2012;8: 713–22. https://doi.org/10.2217/fon.12.59.

[8] Kitadai Y, et al. Transfection of interleukin-8 increases angiogenesis and tumorigenesis of human gastric carcinoma cells in nude mice. Br J Cancer 1999; 81:647–53. https://doi.org/10.1038/sj.bjc.6690742.

[9] Teijeira A, et al. IL8, neutrophils, and NETs in a collusion against cancer immunity and immunotherapy. Clin Cancer Res 2021;27:2383–93. https://doi.org/10.1158/1078-0432.Ccr-20-1319.

[10] Chen Y, et al. IL-8 activates fibroblasts to promote the invasion of HNSCC cells via STAT3-MMP1. Cell Death Discov 2024;10:65. https://doi.org/10.1038/s41420-024-01833-7.

[11] Mao FY, et al. CD45(+)CD33(low)CD11b(dim) myeloid-derived suppressor cells suppress CD8(+) T cell activity via the IL-6/IL-8-arginase I axis in human gastric cancer. Cell Death Dis 2018;9:763. https://doi.org/10.1038/s41419-018-0803-7.

[12] Zhang M, et al. Association of polymorphisms in interleukin-8 gene with cancer risk: a meta-analysis of 22 case-control studies. Onco Targets Ther 2016;9: 3727–37. https://doi.org/10.2147/ott.S103159.

[13] Wang N, et al. 251 t/a polymorphism of the interleukin-8 gene and cancer risk: a HuGE review and meta-analysis based on 42 case-control studies. Mol Biol Rep 2012;39:2831–41. https://doi.org/10.1007/s11033-011-1042-5.

[14] Lurje I, et al. Genetic variant of CXCR1 (rs2234671) associates with clinical outcome in perihilar cholangiocarcinoma. Liver Cancer 2022;11:162–73. https://doi.org/10.1159/000521613.

[15] Gallegos-Arreola MP, et al. The rs1008562, rs2234671, and rs3138060 polymorphisms of the CXCR1 gene are associated with breast cancer risk in a Mexican population. Eur Rev Med Pharmacol Sci 2020;24:9990–10002. https://doi.org/10.26355/eurrev_202010_23212.

[16] Zhou J, et al. Impacts of chemokine (C-X-C motif) receptor 2 C1208T polymorphism on cancer susceptibility. J Immunol Res 2021;2021:8727924. https://doi.org/10.1155/2021/8727924.

[17] Snoussi K, et al. Combined effects of IL-8 and CXCR2 gene polymorphisms on breast cancer susceptibility and aggressiveness. BMC Cancer 2010;10:283. https://doi.org/10.1186/1471-2407-10-283.

[18] Suenaga M, et al. Serum IL-8 level as a candidate prognostic marker of response to anti-angiogenic therapy for metastatic colorectal cancer. Int J Colorectal Dis 2021;36:131–9. https://doi.org/10.1007/s00384-020-03748-y.

[19] Marisi G, et al. IL-8 and thrombospondin-1 as prognostic markers in patients with metastatic colorectal cancer receiving bevacizumab. Cancer Manag Res 2018;10: 5659–66. https://doi.org/10.2147/cmar.S181570.

[20] Tabernero J, et al. Analysis of circulating DNA and protein biomarkers to predict the clinical activity of regorafenib and assess prognosis in patients with metastatic colorectal cancer: a retrospective, exploratory analysis of the CORRECT trial. Lancet Oncol 2015;16:937–48. https://doi.org/10.1016/s1470-2045(15)00138-2.

[21] Hamilton TD, et al. Identification of prognostic inflammatory factors in colorectal liver metastases. BMC Cancer 2014;14:542. https://doi.org/10.1186/1471-2407-14-542.

[22] Liu Y, et al. Correlation of angiogenic biomarker signatures with clinical outcomes in metastatic colorectal cancer patients receiving capecitabine, oxaliplatin, and bevacizumab. Cancer Med 2013;2:234–42. https://doi.org/10.1002/cam4.71.

[23] Spencer SK, et al. Prognostic/predictive value of 207 serum factors in colorectal cancer treated with cediranib and/or chemotherapy. Br J Cancer 2013;109: 2765–73. https://doi.org/10.1038/bjc.2013.649.

[24] Bruhn MA, et al. Proangiogenic tumor proteins as potential predictive or prognostic biomarkers for bevacizumab therapy in metastatic colorectal cancer. Int J Cancer 2014;135:731–41. https://doi.org/10.1002/ijc.28698.

[25] Carril-Ajuria L, et al. High circulating IL-6/IL-8 is associated with intratumoral myeloid contexture and poor outcomes in patients with advanced renal cell carcinoma treated with PD-1 blockade. Clin Cancer Res 2025;31:4150–8. https://doi.org/10.1158/1078-0432.Ccr-24-0902.

[26] Lin Y, Liao Y, Huang M, Shen J. Elevated circulating IL-8 correlates with poor prognosis in urological cancers: a meta-analysis and bioinformatic validation. Ann Med 2025;57:2486592. https://doi.org/10.1080/07853890.2025.2486592.

[27] Powles T, et al. Outcomes based on plasma biomarkers in METEOR, a randomized phase 3 trial of cabozantinib vs everolimus in advanced renal cell carcinoma. BMC Cancer 2021;21:904. https://doi.org/10.1186/s12885-021-08630-w.

[28] Maynard JP, et al. IL8 expression is associated with prostate cancer aggressiveness and androgen receptor loss in primary and metastatic prostate cancer. Mol Cancer Res 2020;18:153–65. https://doi.org/10.1158/1541-7786.Mcr-19-0595.

[29] Yuen KC, et al. High systemic and tumor-associated IL-8 correlates with reduced clinical benefit of PD-L1 blockade. Nat Med 2020;26:693–8. https://doi.org/10.1038/s41591-020-0860-1.

[30] Harshman LC, et al. Impact of baseline serum IL-8 on metastatic hormone-sensitive prostate cancer outcomes in the phase 3 CHAARTED trial (E3805). Prostate 2020;80:1429–37. https://doi.org/10.1002/pros.24074.

[31] Schalper KA, et al. Elevated serum interleukin-8 is associated with enhanced intratumor neutrophils and reduced clinical benefit of immune-checkpoint inhibitors. Nat Med 2020;26:688–92. https://doi.org/10.1038/s41591-020-0856-x.

[32] Msaouel P, Zurita AJ, Huang S, Jonasch E, Tannir NM. Plasma cytokine and angiogenic factors associated with prognosis and therapeutic response to sunitinib vs everolimus in advanced non-clear cell renal cell carcinoma. Oncotarget 2017;8:42149–58. https://doi.org/10.18632/oncotarget.15011.

[33] Bilen MA, et al. Hypertension and circulating cytokines and angiogenic factors in patients with advanced non-clear cell renal cell carcinoma treated with sunitinib: results from a phase II trial. Oncologist 2015;20:1140–8. https://doi.org/10.1634/theoncologist.2015-0143.

[34] Sharma J, et al. Elevated IL-8, TNF-α, and MCP-1 in men with metastatic prostate cancer starting androgen-deprivation therapy (ADT) are associated with shorter time to castration-resistance and overall survival. Prostate 2014;74:820–8. https://doi.org/10.1002/pros.22788.

[35] Harmon CS, et al. Circulating proteins as potential biomarkers of sunitinib and interferon-α efficacy in treatment-naïve patients with metastatic renal cell carcinoma. Cancer Chemother Pharmacol 2014;73:151–61. https://doi.org/10.1007/s00280-013-2333-4.

[36] Rice SJ, Belani CP. Diversity and heterogeneity of immune states in non-small cell lung cancer and small cell lung cancer. PLoS One 2021;16:e0260988. https://doi.org/10.1371/journal.pone.0260988.

[37] Shi Y, et al. Circulating cytokines associated with clinical outcomes in advanced non-small cell lung cancer patients who received chemoimmunotherapy. Thorac Cancer 2022;13:219–27. https://doi.org/10.1111/1759-7714.14248.

[38] Kauffmann-Guerrero D, et al. Systemic inflammation and pro-inflammatory cytokine profile predict response to checkpoint inhibitor treatment in NSCLC: a prospective study. Sci Rep 2021;11:10919. https://doi.org/10.1038/s41598-021-90397-y.

[39] Zhou J, et al. Impact of chronic obstructive pulmonary disease on immune checkpoint inhibitor efficacy in advanced lung cancer and the potential prognostic factors. Transl Lung Cancer Res 2021;10:2148–62. https://doi.org/10.21037/tlcr-21-214.

[40] Sui X, et al. Prediction of clinical outcome in locally advanced non-small cell lung cancer patients treated with chemoradiotherapy by plasma markers. Front Oncol 2020;10:625911. https://doi.org/10.3389/fonc.2020.625911.

[41] Gu L, Yao Y, Chen Z. An inter-correlation among chemokine (C-X-C motif) ligand (CXCL) 1, CXCL2 and CXCL8, and their diversified potential as biomarkers for tumor features and survival profiles in non-small cell lung cancer patients. Transl Cancer Res 2021;10:748–58. https://doi.org/10.21037/tcr-20-2539.

[42] Hardy-Werbin M, et al. Serum cytokine levels as predictive biomarkers of benefit from ipilimumab in small cell lung cancer. Oncoimmunology 2019;8:e1593810. https://doi.org/10.1080/2162402x.2019.1593810.

[43] Fidler MJ, et al. Differential expression of circulating biomarkers of tumor phenotype and outcomes in previously treated non-small cell lung cancer patients receiving erlotinib vs. cytotoxic chemotherapy. Oncotarget 2017;8:58108–21. https://doi.org/10.18632/oncotarget.17510.

[44] Cheng D, Kong H, Li Y. Prognostic values of VEGF and IL-8 in malignant pleural effusion in patients with lung cancer. Biomarkers 2013;18:386–90. https://doi.org/10.3109/1354750x.2013.797499.

[45] Ryan BM, Pine SR, Chaturvedi AK, Caporaso N, Harris CC. A combined prognostic serum interleukin-8 and interleukin-6 classifier for stage 1 lung cancer in the

prostate, lung, colorectal, and ovarian cancer screening trial. J Thorac Oncol 2014;9:1494–503. https://doi.org/10.1097/jto.0000000000000278.
[46] Seike M, et al. Use of a cytokine gene expression signature in lung adenocarcinoma and the surrounding tissue as a prognostic classifier. J Natl Cancer Inst 2007;99:1257–69. https://doi.org/10.1093/jnci/djm083.
[47] Orditura M, et al. Elevated serum levels of interleukin-8 in advanced non-small cell lung cancer patients: relationship with prognosis. J Interferon Cytokine Res 2002;22:1129–35. https://doi.org/10.1089/10799900260442557.
[48] Madsen CO, et al. Peripheral immune biomarkers associated with response to adoptive cell therapy with tumor infiltrating lymphocytes. Clin Exp Immunol 2025;219. https://doi.org/10.1093/cei/uxaf010.
[49] Levati L, et al. Circulating interleukin-8 and osteopontin are promising biomarkers of clinical outcomes in advanced melanoma patients treated with targeted therapy. J Exp Clin Cancer Res 2024;43:226. https://doi.org/10.1186/s13046-024-03151-3.
[50] Pedersen JG, et al. Inflammatory cytokines and ctDNA are biomarkers for progression in advanced-stage melanoma patients receiving checkpoint inhibitors. Cancers (Basel) 2020;12. https://doi.org/10.3390/cancers12061414.
[51] Lim SY, et al. Circulating cytokines predict immune-related toxicity in melanoma patients receiving anti-PD-1-based immunotherapy. Clin Cancer Res 2019;25:1557–63. https://doi.org/10.1158/1078-0432.Ccr-18-2795.
[52] Jamal R, et al. Peripheral and local predictive immune signatures identified in a phase II trial of ipilimumab with carboplatin/paclitaxel in unresectable stage III or stage IV melanoma. J Immunother Cancer 2017;5:83. https://doi.org/10.1186/s40425-017-0290-x.
[53] Sanmamed MF, et al. Changes in serum interleukin-8 (IL-8) levels reflect and predict response to anti-PD-1 treatment in melanoma and non-small-cell lung cancer patients. Ann Oncol 2017;28:1988–95. https://doi.org/10.1093/annonc/mdx190.
[54] Sanmamed MF, et al. Serum interleukin-8 reflects tumor burden and treatment response across malignancies of multiple tissue origins. Clin Cancer Res 2014;20:5697–707. https://doi.org/10.1158/1078-0432.Ccr-13-3203.
[55] Hutajulu SH, et al. High IL-8 plasma levels at baseline are predictive of poor overall survival in breast cancer patients receiving chemotherapy. BMC Res Notes 2025;18:283. https://doi.org/10.1186/s13104-025-07353-6.
[56] Gunnarsdottir FB, et al. Serum immuno-oncology markers carry independent prognostic information in patients with newly diagnosed metastatic breast cancer, from a prospective observational study. Breast Cancer Res 2023;25:29. https://doi.org/10.1186/s13058-023-01631-6.
[57] Tiainen L, et al. Low plasma IL-8 levels during chemotherapy are predictive of excellent long-term survival in metastatic breast cancer. Clin Breast Cancer 2019;19:e522–33. https://doi.org/10.1016/j.clbc.2019.03.006.
[58] Benoy IH, et al. Increased serum interleukin-8 in patients with early and metastatic breast cancer correlates with early dissemination and survival. Clin Cancer Res 2004;10:7157–62. https://doi.org/10.1158/1078-0432.Ccr-04-0812.
[59] Dobrzycka B, et al. Serum levels of IL-6, IL-8 and CRP as prognostic factors in epithelial ovarian cancer. Eur Cytokine Netw 2013;24:106–13. https://doi.org/10.1684/ecn.2013.0340.
[60] Aune G, et al. Circulating interleukin-8 and plasminogen activator inhibitor-1 are increased in women with ovarian carcinoma. Results Immunol 2012;2:190–5. https://doi.org/10.1016/j.rinim.2012.10.003.
[61] Merritt WM, et al. Effect of interleukin-8 gene silencing with liposome-encapsulated small interfering RNA on ovarian cancer cell growth. J Natl Cancer Inst 2008;100:359–72. https://doi.org/10.1093/jnci/djn024.
[62] Röhl L, et al. Immune checkpoint blockade induced shifts in cytokine expression patterns in peripheral blood of head and neck cancer patients are linked to outcome. Front Immunol 2023;14:1237623. https://doi.org/10.3389/fimmu.2023.1237623.
[63] Fujita Y, et al. Prognostic significance of interleukin-8 and CD163-positive cell-infiltration in tumor tissues in patients with oral squamous cell carcinoma. PLoS One 2014;9:e110378. https://doi.org/10.1371/journal.pone.0110378.
[64] Conciatori F, et al. BRAF status modulates Interelukin-8 expression through a CHOP-dependent mechanism in colorectal cancer. Commun Biol 2020;3. https://doi.org/10.1038/s42003-020-01263-y.
[65] Bazzichetto C, et al. Interleukin-8 in colorectal cancer: a systematic review and meta-analysis of its potential role as a prognostic biomarker. Biomedicines 2022;10. https://doi.org/10.3390/biomedicines10102631.
[66] Conciatori F, et al. Colorectal cancer stem cells properties and features: evidence of interleukin-8 involvement. Cancer Drug Resist 2019;2:968–79. https://doi.org/10.20517/cdr.2019.56.
[67] Cui G, Wang Z, Liu H, Pang Z. Cytokine-mediated crosstalk between cancer stem cells and their inflammatory niche from the colorectal precancerous adenoma stage to the cancerous stage: Mechanisms and clinical implications. Front Immunol 2022;13:1057181. https://doi.org/10.3389/fimmu.2022.1057181.
[68] Xia W, et al. Prognostic value, clinicopathologic features and diagnostic accuracy of interleukin-8 in colorectal cancer: a meta-analysis. PLoS One 2015;10:e0123484. https://doi.org/10.1371/journal.pone.0123484.
[69] Lurje G, et al. Polymorphisms in VEGF and IL-8 predict tumor recurrence in stage III colon cancer. Ann Oncol 2008;19:1734–41. https://doi.org/10.1093/annonc/mdn368.
[70] Inoue M, et al. IL-8/CXCR2 signalling promotes cell proliferation in oesophageal squamous cell carcinoma and correlates with poor prognosis. Anticancer Res 2021;41:783–94. https://doi.org/10.21873/anticanres.14830.
[71] Ogura M, et al. Clinical significance of CXCL-8/CXCR-2 network in esophageal squamous cell carcinoma. Surgery 2013;154:512–20. https://doi.org/10.1016/j.surg.2013.06.013.
[72] Łukaszewicz-Zając M, Pączek S, Mroczko B. The significance of chemokine CXCL-8 in esophageal carcinoma. Arch Med Sci 2020;16:475–80. https://doi.org/10.5114/aoms.2017.71933.
[73] Xu B, Yan Y. The association between IL-8 gene polymorphisms and the risk of several types of cancer. Especially in Gastric Cancer Cancer Rep (Hoboken) 2025;8:e70103. https://doi.org/10.1002/cnr2.70103.
[74] Lurje G, et al. Genetic variations in angiogenesis pathway genes associated with clinical outcome in localized gastric adenocarcinoma. Ann Oncol 2010;21:78–86. https://doi.org/10.1093/annonc/mdp280.
[75] Kuwada Y, et al. Potential involvement of IL-8 and its receptors in the invasiveness of pancreatic cancer cells. Int J Oncol 2003;22:765–71.
[76] Litman-Zawadzka A, Łukaszewicz-Zając M, Gryko M, Kulczyńska-Przybik A, Mroczko B. Serum chemokine CXCL8 as a better biomarker for diagnosis and prediction of pancreatic cancer than its specific receptor CXCR2, C-reactive protein, and classic tumor markers CA 19-9 and CEA. Pol Arch Intern Med 2018;128:524–31. https://doi.org/10.20452/pamw.4307.
[77] Feng L, et al. Serum levels of IL-6, IL-8, and IL-10 are indicators of prognosis in pancreatic cancer. J Int Med Res 2018;46:5228–36. https://doi.org/10.1177/0300060518800588.
[78] Merz V, et al. Plasma IL8 is a biomarker for TAK1 activation and predicts resistance to nanoliposomal irinotecan in patients with gemcitabine-refractory pancreatic cancer. Clin Cancer Res 2020;26:4661–9. https://doi.org/10.1158/1078-0432.Ccr-20-0395.
[79] Wang JL, et al. Association of interleukin-8 gene polymorphisms with the risk of hepatocellular carcinoma. Mol Biol Rep 2014;41:1483–9. https://doi.org/10.1007/s11033-013-2993-5.
[80] Yang S, Wang H, Qin C, Sun H, Han Y. Up-regulation of CXCL8 expression is associated with a poor prognosis and enhances tumor cell malignant behaviors in liver cancer. Biosci Rep 2020;40. https://doi.org/10.1042/bsr20201169.
[81] Deng Y, et al. High interleukin-8 and/or extracellular signal-regulated kinase 2 expression predicts poor prognosis in patients with hepatocellular carcinoma. Oncol Lett 2019;18:5215–24. https://doi.org/10.3892/ol.2019.10907.
[82] Lurje I, et al. Genetic polymorphisms in interleukin-1β (rs1143634) and interleukin-8 (rs4073) are associated with survival after resection of intrahepatic cholangiocarcinoma. Sci Rep 2023;13:12283. https://doi.org/10.1038/s41598-023-39487-7.
[83] Sunaga N, et al. Oncogenic KRAS-induced interleukin-8 overexpression promotes cell growth and migration and contributes to aggressive phenotypes of non-small cell lung cancer. Int J Cancer 2012;130:1733–44. https://doi.org/10.1002/ijc.26164.
[84] Sparmann A, Bar-Sagi D. Ras-induced interleukin-8 expression plays a critical role in tumor growth and angiogenesis. Cancer Cell 2004;6:447–58. https://doi.org/10.1016/j.ccr.2004.09.028.
[85] Sunaga N, et al. Clinicopathological and prognostic significance of interleukin-8 expression and its relationship to KRAS mutation in lung adenocarcinoma. Br J Cancer 2014;110:2047–53. https://doi.org/10.1038/bjc.2014.110.
[86] Liu YN, et al. IL-8 confers resistance to EGFR inhibitors by inducing stem cell properties in lung cancer. Oncotarget 2015;6:10415–31. https://doi.org/10.18632/oncotarget.3389.
[87] Wu J, et al. IL-8 from CD248-expressing cancer-associated fibroblasts generates cisplatin resistance in non-small cell lung cancer. J Cell Mol Med 2024;28:e18185. https://doi.org/10.1111/jcmm.18185.
[88] Cury SS, et al. Tumor transcriptome reveals high expression of IL-8 in non-small cell lung cancer patients with low pectoralis muscle area and reduced survival. Cancers (Basel) 2019;11. https://doi.org/10.3390/cancers11091251.
[89] Belluomini L, et al. Prognostic impact of Interleukin-8 levels in lung cancer: a meta-analysis and a bioinformatic validation. Lung Cancer 2024;194:107893. https://doi.org/10.1016/j.lungcan.2024.107893.
[90] Milosevic V, et al. Wnt/IL-1β/IL-8 autocrine circuitries control chemoresistance in mesothelioma initiating cells by inducing ABCB5. Int J Cancer 2020;146:192–207. https://doi.org/10.1002/ijc.32419.
[91] Gao S, et al. Interleukin-8 as a candidate for thymoma identification and recurrence surveillance. Nat Commun 2020;11:4881. https://doi.org/10.1038/s41467-020-18697-x.
[92] Lopez-Bujanda ZA, et al. Castration-mediated IL-8 promotes myeloid infiltration and prostate cancer progression. Nat Cancer 2021;2:803–18. https://doi.org/10.1038/s43018-021-00227-3.
[93] Xu F, et al. Prostate cancer cell-derived exosomal IL-8 fosters immune evasion by disturbing glucolipid metabolism of CD8(+) T cell. Cell Rep 2023;42:113424. https://doi.org/10.1016/j.celrep.2023.113424.
[94] Beckabir W, et al. Immune features are associated with response to neoadjuvant chemo-immunotherapy for muscle-invasive bladder cancer. Nat Commun 2024;15:4448. https://doi.org/10.1038/s41467-024-48480-1.
[95] Zacchi F, et al. Interleukin-8 as a potential prognostic biomarker in renal cell carcinoma: a systematic review and meta-analysis. Oncologist 2025;30. https://doi.org/10.1093/oncolo/oyaf254.
[96] Yang ES, et al. Kinase analysis of penile squamous cell carcinoma on multiple platforms to identify potential therapeutic targets. Oncotarget 2017;8:21710–8. https://doi.org/10.18632/oncotarget.15558.
[97] Kunz M, et al. Anoxia-induced up-regulation of interleukin-8 in human malignant melanoma. a potential mechanism for high tumor aggressiveness. Am J Pathol 1999;155:753–63. https://doi.org/10.1016/s0002-9440(10)65174-7.
[98] Ramjeesingh R, Leung R, Siu CH. Interleukin-8 secreted by endothelial cells induces chemotaxis of melanoma cells through the chemokine receptor CXCR1. FASEB J 2003;17:1292–4. https://doi.org/10.1096/fj.02-0560fje.

[99] Bourcier C, et al. Constitutive ERK activity induces downregulation of tristetraprolin, a major protein controlling interleukin8/CXCL8 mRNA stability in melanoma cells. Am J Physiol Cell Physiol 2011;301:C609–18. https://doi.org/10.1152/ajpcell.00506.2010.
[100] Conciatori F, et al. BRAF status modulates Interelukin-8 expression through a CHOP-dependent mechanism in colorectal cancer. Commun Biol 2020;3:546. https://doi.org/10.1038/s42003-020-01263-y.
[101] Singh S, Varney M, Singh RK. Host CXCR2-dependent regulation of melanoma growth, angiogenesis, and experimental lung metastasis. Cancer Res 2009;69:411–5. https://doi.org/10.1158/0008-5472.Can-08-3378.
[102] Gabellini C, et al. Functional activity of CXCL8 receptors, CXCR1 and CXCR2, on human malignant melanoma progression. Eur J Cancer 2009;45:2618–27. https://doi.org/10.1016/j.ejca.2009.07.007.
[103] Singh S, Singh AP, Sharma B, Owen LB, Singh RK. CXCL8 and its cognate receptors in melanoma progression and metastasis. Future Oncol 2010;6:111–6. https://doi.org/10.2217/fon.09.128.
[104] Varney ML, et al. Expression of CXCR1 and CXCR2 receptors in malignant melanoma with different metastatic potential and their role in interleukin-8 (CXCL-8)-mediated modulation of metastatic phenotype. Clin Exp Metastasis 2003;20:723–31. https://doi.org/10.1023/b:clin.0000006814.48627.bd.
[105] Hong A, et al. Lnc-PKNOX1-1 inhibits tumor progression in cutaneous malignant melanoma by regulating NF-κB/IL-8 axis. Carcinogenesis 2023;44:871–83. https://doi.org/10.1093/carcin/bgad073.
[106] Su W, et al. Bioinformatic analysis reveals hub genes and pathways that promote melanoma metastasis. BMC Cancer 2020;20:863. https://doi.org/10.1186/s12885-020-07372-5.
[107] Wilson BJ, et al. ABCB5 maintains melanoma-initiating cells through a proinflammatory cytokine signaling circuit. Cancer Res 2014;74:4196–207. https://doi.org/10.1158/0008-5472.Can-14-0582.
[108] Hartman ML, Rozanski M, Osrodek M, Zalesna I, Czyz M. Vemurafenib and trametinib reduce expression of CTGF and IL-8 in (V600E)BRAF melanoma cells. Lab Invest 2017;97:217–27. https://doi.org/10.1038/labinvest.2016.140.
[109] Mishra A, Suman KH, Nair N, Majeed J, Tripathi V. An updated review on the role of the CXCL8-CXCR1/2 axis in the progression and metastasis of breast cancer. Mol Biol Rep 2021;48:6551–61. https://doi.org/10.1007/s11033-021-06648-8.
[110] Huang R, et al. Targeting cancer-associated adipocyte-derived CXCL8 inhibits triple-negative breast cancer progression and enhances the efficacy of anti-PD-1 immunotherapy. Cell Death Dis 2023;14:703. https://doi.org/10.1038/s41419-023-06230-z.
[111] De Larco JE, et al. A potential role for interleukin-8 in the metastatic phenotype of breast carcinoma cells. Am J Pathol 2001;158:639–46. https://doi.org/10.1016/s0002-9440(10)64005-9.
[112] Ruffini PA. The CXCL8-CXCR1/2 axis as a therapeutic target in breast cancer stem-like cells. Front Oncol 2019;9:40. https://doi.org/10.3389/fonc.2019.00040.
[113] Shao N, Chen LH, Ye RY, Lin Y, Wang SM. The depletion of interleukin-8 causes cell cycle arrest and increases the efficacy of docetaxel in breast cancer cells. Biochem Biophys Res Commun 2013;431:535–41. https://doi.org/10.1016/j.bbrc.2013.01.022.
[114] Shi Z, et al. Enhanced chemosensitization in multidrug-resistant human breast cancer cells by inhibition of IL-6 and IL-8 production. Breast Cancer Res Treat 2012;135:737–47. https://doi.org/10.1007/s10549-012-2196-0.
[115] Lin HY, et al. The IL-8/NF-κB feedback loop confers a paclitaxel-sensitive/doxorubicin-resistant phenotype in triple-negative breast cancer. Free Radic Biol Med 2025;238:316–28. https://doi.org/10.1016/j.freeradbiomed.2025.06.049.
[116] Liao H, et al. Expression of the prognostic marker IL-8 correlates with the immune signature and epithelial-mesenchymal transition in breast cancer. J Clin Lab Anal 2023;37:e24797. https://doi.org/10.1002/jcla.24797.
[117] Ishikawa E, et al. The cytokine profile correlates with less tumor-infiltrating lymphocytes in luminal a breast cancer. Breast Cancer Res Treat 2025;209:291–302. https://doi.org/10.1007/s10549-024-07492-7.
[118] Todorović-Raković N, Milovanović J. Interleukin-8 in breast cancer progression. J Interferon Cytokine Res 2013;33:563–70. https://doi.org/10.1089/jir.2013.0023.
[119] Milovanović J, Todorović-Raković N, Radulovic M. Interleukin-6 and interleukin-8 serum levels in prognosis of hormone-dependent breast cancer. Cytokine 2019;118:93–8. https://doi.org/10.1016/j.cyto.2018.02.019.
[120] Kamalakar A, et al. Circulating interleukin-8 levels explain breast cancer osteolysis in mice and humans. Bone 2014;61:176–85. https://doi.org/10.1016/j.bone.2014.01.015.
[121] Derin D, et al. Serum IL-8 and IL-12 levels in breast cancer. Med Oncol 2007;24:163–8. https://doi.org/10.1007/bf02698035.
[122] Tang S, Zhang Y, Song L, Hui K, Jiang X. High CXCL8 expression predicting poor prognosis in triple-negative breast cancer. Anticancer Drugs 2025;36:246–52. https://doi.org/10.1097/cad.0000000000001678.
[123] Milovanovic J, Todorovic-Rakovic N, Vujasinovic T, Abu Rabi Z. Interleukin 8 in progression of hormone-dependent early breast cancer. J Biosci 2017;42:265–74. https://doi.org/10.1007/s12038-017-9679-4.
[124] Milovanovic J, Todorovic-Rakovic N, Abu Rabi Z. The prognostic role of interleukin-8 (IL-8) and matrix metalloproteinases -2 and -9 in lymph node-negative untreated breast cancer patients. J BUON 2013;18:866–73.
[125] Zuccari DA, et al. An immunohistochemical study of interleukin-8 (IL-8) in breast cancer. Acta Histochem 2012;114:571–6. https://doi.org/10.1016/j.acthis.2011.10.007.
[126] Chen E, et al. Identification of potential therapeutic targets among CXC chemokines in breast tumor microenvironment using integrative bioinformatics analysis. Cell Physiol Biochem 2018;45:1731–46. https://doi.org/10.1159/000487782.
[127] Fang QI, et al. Increased CXCL8 expression is negatively correlated with the overall survival of patients with ER-negative breast cancer. Anticancer Res 2017;37:4845–52. https://doi.org/10.21873/anticanres.11892.
[128] Kirkegaard C, et al. Effect of one year continuous subcutaneous infusion of a somatostatin analogue, octreotide, on early retinopathy, metabolic control and thyroid function in Type I (insulin-dependent) diabetes mellitus. Acta Endocrinol (Copenh) 1990;122:766–72. https://doi.org/10.1530/acta.0.1220766.
[129] Foldi J, et al. Peripheral blood immune parameters, response, and adverse events after neoadjuvant chemotherapy plus durvalumab in early-stage triple-negative breast cancer. Breast Cancer Res Treat 2024;208:369–77. https://doi.org/10.1007/s10549-024-07426-3.
[130] Wang RX, Ji P, Gong Y, Shao ZM, Chen S. Value of CXCL8-CXCR1/2 axis in neoadjuvant chemotherapy for triple-negative breast cancer patients: a retrospective pilot study. Breast Cancer Res Treat 2020;181:561–70. https://doi.org/10.1007/s10549-020-05660-z.
[131] Merlano MC, et al. Cytokine profiling of end stage cancer patients treated with immunotherapy. Vaccines (Basel) 2021;9. https://doi.org/10.3390/vaccines9030235.
[132] Liu J, et al. Biomarkers of response to camrelizumab combined with apatinib: an analysis from a phase II trial in advanced triple-negative breast cancer patients. Breast Cancer Res Treat 2021;186:687–97. https://doi.org/10.1007/s10549-021-06128-4.
[133] Garrone O, et al. Exploratory analysis of circulating cytokines in patients with metastatic breast cancer treated with eribulin: the TRANSERI-GONO (Gruppo Oncologico del Nord Ovest) study. ESMO Open 2020;5:e000876. https://doi.org/10.1136/esmoopen-2020-000876.
[134] Xu Q, et al. The interaction of interleukin-8 and PTEN inactivation promotes the malignant progression of head and neck squamous cell carcinoma via the STAT3 pathway. Cell Death Dis 2020;11:405. https://doi.org/10.1038/s41419-020-2627-5.
[135] Joshi S, Pandey R, Kumar A, Gupta V, Arya N. Targeted blockade of interleukin-8 negates metastasis and chemoresistance via Akt/Erk-NFκB axis in oral cancer. Cytokine 2023;166:156155. https://doi.org/10.1016/j.cyto.2023.156155.
[136] Xu Q, et al. Downregulation of VAP-1 in OSCC suppresses tumor growth and metastasis via NF-κB/IL-8 signaling and reduces neutrophil infiltration. J Oral Pathol Med 2022;51:332–41. https://doi.org/10.1111/jop.13285.
[137] Zeng C, et al. Downregulation of FOXP3 in neutrophils by IL-8 promotes the progression of oral squamous cell carcinoma. Oncol Lett 2019;18:4771–7. https://doi.org/10.3892/ol.2019.10828.
[138] Kai K, et al. Oral squamous cell carcinoma contributes to differentiation of monocyte-derived tumor-associated macrophages via PAI-1 and IL-8 production. Int J Mol Sci 2021;22. https://doi.org/10.3390/ijms22179475.
[139] Horn LA, et al. Inhibition of the chemokine receptors CXCR1 and CXCR2 synergizes with docetaxel for effective tumor control and remodeling of the immune microenvironment of HPV-negative head and neck cancer models. J Exp Clin Cancer Res 2024;43:318. https://doi.org/10.1186/s13046-024-03240-3.
[140] Hao W, Zhu Y, Zhou H. Prognostic value of interleukin-6 and interleukin-8 in laryngeal squamous cell cancer. Med Oncol 2013;30:333. https://doi.org/10.1007/s12032-012-0333-6.
[141] Eyigor M, et al. Analysis of serum cytokine levels in larynx squamous cell carcinoma and dysplasia patients. Iran J Immunol 2014;11:259–68.
[142] Linkov F, et al. Early detection of head and neck cancer: development of a novel screening tool using multiplexed immunobead-based biomarker profiling. Cancer Epidemiol Biomarkers Prev 2007;16:102–7. https://doi.org/10.1158/1055-9965.Epi-06-0602.
[143] Mojtahedi Z, et al. Serum levels of interleukin-7 and interleukin-8 in head and neck squamous cell carcinoma. Indian J Cancer 2014;51:227–30. https://doi.org/10.4103/0019-509x.146728.
[144] Hong DY, et al. Expression of VEGF, HGF, IL-6, IL-8, MMP-9, telomerase in peripheral blood of patients with head and neck squamous cell carcinoma. Clin Exp Otorhinolaryngol 2009;2:186–92. https://doi.org/10.3342/ceo.2009.2.4.186.
[145] Brøndum L, et al. Plasma proteins as prognostic biomarkers in radiotherapy treated head and neck cancer patients. Clin Transl Radiat Oncol 2017;2:46–52. https://doi.org/10.1016/j.ctro.2017.01.001.
[146] Le QT, et al. Prognostic and predictive significance of plasma HGF and IL-8 in a phase III trial of chemoradiation with or without tirapazamine in locoregionally advanced head and neck cancer. Clin Cancer Res 2012;18:1798–807. https://doi.org/10.1158/1078-0432.Ccr-11-2094.
[147] Astradsson T, Sellberg F, Berglund D, Ehrsson YT, Laurell GFE. Systemic inflammatory reaction in patients with head and neck cancer-an explorative study. Front Oncol 2019;9:1177. https://doi.org/10.3389/fonc.2019.01177.
[148] León X, et al. Predictive capacity of IL-8 expression in head and neck squamous carcinoma patients treated with radiotherapy or chemoradiotherapy. Acta Otorrinolaringol Esp (Engl Ed) 2021;72:337–43. https://doi.org/10.1016/j.otoeng.2020.05.006.
[149] Jing F, et al. Bioinformatics analysis of the role of CXC ligands in the microenvironment of head and neck tumor. Aging (Albany NY) 2021;13:17789–817. https://doi.org/10.18632/aging.203269.
[150] Zhao Z, et al. Expression of chemokine CXCL8/9/10/11/13 and its prognostic significance in head and neck cancer. Medicine (Baltimore) 2022;101:e29378. https://doi.org/10.1097/md.0000000000029378.

[151] Green VL, Michno A, Greenman J, Stafford ND. Effect of treatment on systemic cytokines in head and neck squamous cell carcinoma patients. Results Immunol 2011;2:1–6. https://doi.org/10.1016/j.rinim.2011.12.001.
[152] Hill BL, et al. IL-8 correlates with nonresponse to neoadjuvant nivolumab in HPV positive HNSCC via a potential extracellular vesicle miR-146a mediated mechanism. Mol Carcinog 2023;62:1428–43. https://doi.org/10.1002/mc.23587.
[153] Huldani H, et al. The potential role of interleukins and interferons in ovarian cancer. Cytokine 2023;171:156379. https://doi.org/10.1016/j.cyto.2023.156379.
[154] Stronach EA, et al. The role of interleukin-8 (IL-8) and IL-8 receptors in platinum response in high grade serous ovarian carcinoma. Oncotarget 2015;6:31593–603. https://doi.org/10.18632/oncotarget.3415.
[155] Zhang R, Roque DM, Reader J, Lin J. Combined inhibition of IL-6 and IL-8 pathways suppresses ovarian cancer cell viability and migration and tumor growth. Int J Oncol 2022;60. https://doi.org/10.3892/ijo.2022.5340.
[156] Ren M, Chen LL, Jiang LY, Yu HH, Ji HZ. The CXCL8-CXCR2 axis promotes M2 macrophage polarization in ovarian cancer via RASGRP4-mediated mTOR-STAT3 signaling. Apoptosis 2025;30:1839–51. https://doi.org/10.1007/s10495-025-02128-7.
[157] Browne A, et al. Differential expression of IL-8 and IL-8 receptors in benign, borderline and malignant ovarian epithelial tumours. Cytokine 2013;64:413–21. https://doi.org/10.1016/j.cyto.2013.05.006.
[158] Lee JM, et al. Phase II trial of bevacizumab and sorafenib in recurrent ovarian cancer patients with or without prior-bevacizumab treatment. Gynecol Oncol 2020;159:88–94. https://doi.org/10.1016/j.ygyno.2020.07.031.
[159] Kassim SK, et al. Vascular endothelial growth factor and interleukin-8 are associated with poor prognosis in epithelial ovarian cancer patients. Clin Biochem 2004;37:363–9. https://doi.org/10.1016/j.clinbiochem.2004.01.014.
[160] Zhang L, Liu W, Wang X, Wang X, Sun H. Prognostic value of serum IL-8 and IL-10 in patients with ovarian cancer undergoing chemotherapy. Oncol Lett 2019;17:2365–9. https://doi.org/10.3892/ol.2018.9842.
[161] Mayerhofer K, et al. Interleukin-8 serum level shift in patients with ovarian carcinoma undergoing paclitaxel-containing chemotherapy. Cancer 2001;91:388–93.
[162] Niu N, et al. Expression of B7-H4 and IDO1 is associated with drug resistance and poor prognosis in high-grade serous ovarian carcinomas. Hum Pathol 2021;113:20–7. https://doi.org/10.1016/j.humpath.2021.04.003.
[163] Pasquier J, et al. Surgical peritoneal stress creates a pro-metastatic niche promoting resistance to apoptosis via IL-8. J Transl Med 2018;16:271. https://doi.org/10.1186/s12967-018-1643-z.
[164] Alfaro C, et al. Interleukin-8 in cancer pathogenesis, treatment and follow-up. Cancer Treat Rev 2017;60:24–31. https://doi.org/10.1016/j.ctrv.2017.08.004.
[165] Rizzo M, et al. IL-8 and its role as a potential biomarker of resistance to anti-angiogenic agents and immune checkpoint inhibitors in metastatic renal cell carcinoma. Front Oncol 2022;12:990568. https://doi.org/10.3389/fonc.2022.990568.
[166] Adamo A, et al. Immune checkpoint blockade therapy mitigates systemic inflammation and affects cellular FLIP-expressing monocytic myeloid-derived suppressor cells in non-progressor non-small cell lung cancer patients. Oncoimmunology 2023;12:2253644. https://doi.org/10.1080/2162402X.2023.2253644.
[167] Harada A, et al. Essential involvement of interleukin-8 (IL-8) in acute inflammation. J Leukoc Biol 1994;56:559–64.
[168] Roebuck KA. Regulation of interleukin-8 gene expression. J Interferon Cytokine Res 1999;19:429–38. https://doi.org/10.1089/107999099313866.
[169] Cesta MC, et al. The role of interleukin-8 in lung inflammation and injury: implications for the management of COVID-19 and hyperinflammatory acute respiratory distress syndrome. Front Pharmacol 2021;12:808797. https://doi.org/10.3389/fphar.2021.808797.
[170] Righi D, et al. Investigating interleukin-8 in Alzheimer's disease: a comprehensive review. J Alzheimers Dis 2025;103:38–55. https://doi.org/10.1177/13872877241298973.
[171] Lisowska KA. The role of interleukin-8 (IL-8) in treatment-resistant depression: a review of mechanisms, biomarker potential, and therapeutic implications. Int J Mol Sci 2025;26. https://doi.org/10.3390/ijms262010092.
[172] Apostolakis S, Vogiatzi K, Amanatidou V, Spandidos DA. Interleukin 8 and cardiovascular disease. Cardiovasc Res 2009;84:353–60. https://doi.org/10.1093/cvr/cvp241.
[173] Clark JA, Peterson TC. Cytokine production and aging: overproduction of IL-8 in elderly males in response to lipopolysaccharide. Mech Ageing Dev 1994;77:127–39. https://doi.org/10.1016/0047-6374(94)90020-5.
[174] Nguyen TQT, Cho KA. Targeting immunosenescence and inflammaging: advancing longevity research. Exp Mol Med 2025;57:1881–92. https://doi.org/10.1038/s12276-025-01527-9.
[175] Coperchini F, et al. Inflamm-ageing: how cytokines and nutrition shape the trajectory of ageing. Cytokine Growth Factor Rev 2025;82:31–42. https://doi.org/10.1016/j.cytogfr.2024.08.004.
[176] Karpuzoglu E, Holladay SD, Gogal Jr RM. Inflammaging: triggers, molecular mechanisms, immunological consequences, sex differences, and cutaneous manifestations. Front Immunol 2025;16:1704203. https://doi.org/10.3389/fimmu.2025.1704203.
[177] Xie H, Wei L, Ruan G, Zhang H, Shi H. Inflammaging score as a potential prognostic tool for cancer: a population-based cohort study. Mech Ageing Dev 2024;219:111939. https://doi.org/10.1016/j.mad.2024.111939.
[178] Esposito D, et al. Early assessment of IL8 and PD1+ Treg predicts response and guides treatment monitoring in cemiplimab-treated cutaneous squamous cell carcinoma. J Immunother Cancer 2025;13. https://doi.org/10.1136/jitc-2024-010421.
[179] Wang Z, et al. Expressivity of interleukin-8 and gastric cancer prognosis susceptibility: a systematic review and meta-analysis. Dose Response 2021;19:15593258211037127. https://doi.org/10.1177/15593258211037127.
[180] Li E, et al. CXCL8 associated dendritic cell activation marker expression and recruitment as indicators of favorable outcomes in colorectal cancer. Front Immunol 2021;12:667177. https://doi.org/10.3389/fimmu.2021.667177.
[181] Oladipo O, et al. The expression and prognostic impact of CXC-chemokines in stage II and III colorectal cancer epithelial and stromal tissue. Br J Cancer 2011;104:480–7. https://doi.org/10.1038/sj.bjc.6606055.
[182] Salvatore L, et al. PTEN in colorectal cancer: shedding light on its role as predictor and target. Cancers (Basel) 2019;11. https://doi.org/10.3390/cancers11111765.
[183] Smycz-Kubańska M, et al. Analysis of CXCL8 and its receptors CXCR1/CXCR2 at the mRNA level in neoplastic tissue, as well as in serum and peritoneal fluid in patients with ovarian cance. Mol Med Rep 2022;26. https://doi.org/10.3892/mmr.2022.12812.
[184] Reddy SU, Sadia FZ, Vancura A, Vancurova I. IFNγ-Induced Bcl3, PD-L1 and IL-8 signaling in ovarian cancer: mechanisms and clinical significance. Cancers (Basel) 2024;16. https://doi.org/10.3390/cancers16152676.
[185] Padmanabhan S, et al. IFNγ induces JAK1/STAT1/p65 NFκB-dependent interleukin-8 expression in ovarian cancer cells, resulting in their increased migration. Int J Biochem Cell Biol 2021;141:106093. https://doi.org/10.1016/j.biocel.2021.106093.
[186] Liu H, et al. Neutralizing IL-8 potentiates immune checkpoint blockade efficacy for glioma. Cancer Cell 2023;41:693–710.e698. https://doi.org/10.1016/j.ccell.2023.03.004.
[187] Singh JK, et al. Targeting CXCR1/2 significantly reduces breast cancer stem cell activity and increases the efficacy of inhibiting HER2 via HER2-dependent and -independent mechanisms. Clin Cancer Res 2013;19:643–56. https://doi.org/10.1158/1078-0432.Ccr-12-1063.
[188] Yang H, et al. Engineered bispecific antibodies targeting the interleukin-6 and -8 receptors potently inhibit cancer cell migration and tumor metastasis. Mol Ther 2022;30:3430–49. https://doi.org/10.1016/j.ymthe.2022.07.008.
[189] Jeong Y, et al. Inhibition of Interleukin-8/C-X-C Chemokine Receptor 2 Signaling Axis Prevents Tumor Growth and Metastasis in Triple-negative Breast Cancer Cells. Pharmacology 2025;110:178–90. https://doi.org/10.1159/000545659.
[190] Abdulkarim S, et al. Role of the IL-8/CXCR2 axis in promoting vasculogenic mimicry in triple-negative breast cancer through epithelial-mesenchymal transition. CP 2024;6. https://doi.org/10.36922/cp.3356.
[191] Bazzichetto C, Di Martile M, Del Bufalo D, Milella M, Conciatori F. Induction of cell death by the CXCR2 antagonist SB225002 in colorectal cancer and stromal cells. Biomed Pharmacother 2025;188:118203. https://doi.org/10.1016/j.biopha.2025.118203.
[192] Huang S, et al. Fully humanized neutralizing antibodies to interleukin-8 (ABX-IL8) inhibit angiogenesis, tumor growth, and metastasis of human melanoma. Am J Pathol 2002;161:125–34. https://doi.org/10.1016/s0002-9440(10)64164-8.
[193] Salcedo R, Martins-Green M, Gertz B, Oppenheim JJ, Murphy WJ. Combined administration of antibodies to human interleukin 8 and epidermal growth factor receptor results in increased antimetastatic effects on human breast carcinoma xenografts. Clin Cancer Res 2002;8:2655–65.
[194] Zippoli M, et al. The role of extracellular vesicles and interleukin-8 in regulating and mediating neutrophil-dependent cancer drug resistance. Front Oncol 2022;12:947183. https://doi.org/10.3389/fonc.2022.947183.
[195] Guo C, et al. Targeting myeloid chemotaxis to reverse prostate cancer therapy resistance. Nature 2023;623:1053–61. https://doi.org/10.1038/s41586-023-06696-z.
[196] Schott AF, et al. Phase Ib pilot study to evaluate reparixin in combination with weekly paclitaxel in patients with HER-2-negative metastatic breast cancer. Clin Cancer Res 2017;23:5358–65. https://doi.org/10.1158/1078-0432.Ccr-16-2748.
[197] Armstrong AJ, et al. CXCR2 antagonist navarixin in combination with pembrolizumab in select advanced solid tumors: a phase 2 randomized trial. Invest New Drugs 2024;42:145–59. https://doi.org/10.1007/s10637-023-01410-2.
[198] Goldstein LJ, et al. A randomized, placebo-controlled phase 2 study of paclitaxel in combination with reparixin compared to paclitaxel alone as front-line therapy for metastatic triple-negative breast cancer (fRida). Breast Cancer Res Treat 2021;190:265–75. https://doi.org/10.1007/s10549-021-06367-5.
[199] M. Simonelli, M. O. B., P.A. Ascierto, G.V. Long, E. Calvo, V. Moreno Garcia, C. Gebhardt, J.J. Grob, A.M. Haydon, G. Quereux, J. Walker, M. Kumar, D. Chakraborty, X. Zhu, I. Melero. 121MO Anti-IL-8 (BMS-986253) in combination with nivolumab (NIVO) plus ipilimumab (IPI) in patients (pts) with advanced melanoma: Final analysis from the randomized part 2 of the phase I/II CA027-002 study. *Immuno-Oncology and Technology* **24** (2024). Doi:10.1016/j.iotech.2024.100750.
[200] Hol J, Wilhelmsen L, Haraldsen G. The murine IL-8 homologues KC, MIP-2, and LIX are found in endothelial cytoplasmic granules but not in Weibel-Palade bodies. J Leukoc Biol 2010;87:501–8. https://doi.org/10.1189/jlb.0809532.

[201] Jiang H, et al. Targeting IL8 as a sequential therapy strategy to overcome chemotherapy resistance in advanced gastric cancer. Cell Death Discov 2022;8: 235. https://doi.org/10.1038/s41420-022-01033-1.
[202] Sharma B, Singh S, Varney ML, Singh RK. Targeting CXCR1/CXCR2 receptor antagonism in malignant melanoma. Expert Opin Ther Targets 2010;14:435–42. https://doi.org/10.1517/14728221003652471.
[203] Jiang H, et al. Targeting IL8 as a sequential therapy strategy to overcome chemotherapy resistance in advanced gastric cancer. Cell Death Discovery 2022; 8. https://doi.org/10.1038/s41420-022-01033-1.