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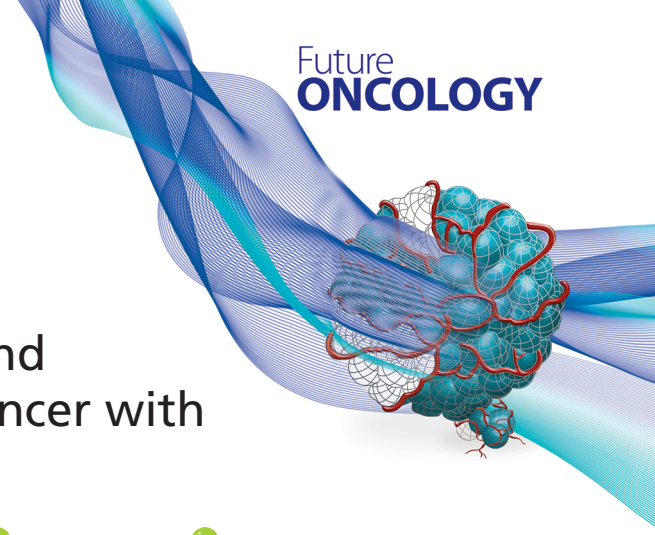

Overcoming immunosuppression and pro-tumor inflammation in lung cancer with combined IL-1β and PD-1 inhibition

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Inflammation in the tumor microenvironment is a complicit and known carcinogenesis driver. Inhibition of IL-1β, one of the most abundant and influential cytokines in the tumor microenvironment, may enhance the efficacy of PD-1. In a *post-hoc* analysis of phase III cardiovascular CANTOS trial, canakinumab, a monoclonal anti-IL-1β antibody, significantly reduced lung cancer incidence. Immune checkpoint inhibition (ICI) is the standard of care in non-small-cell lung cancer. However, ICI efficacy is heavily impacted by programmed death ligand-1 (PD-L1) status. Most patients with non-small-cell lung cancer have low PD-L1 expression levels. Thus, combinational strategies are needed to improve ICI efficacy and expand its use. Here, we describe the preclinical and clinical evidence to support the combination of IL-1β and PD-1 under investigation in the CANOPY program. The perioperative use of canakinumab with or without PD-1 inhibition in the CANOPY-N trial is described as a potential chemotherapy-free immunotherapy strategy.

Plain language summary: IL-1β is a small molecule involved in the spreading of cancer cells and scouting for cells that work against the body's protective inflammatory response. In a follow-up analysis of the CANTOS study, people with atherosclerosis who received canakinumab, a drug which limits the activity of IL-1β in the body, were diagnosed with lung cancer less often than people who received an inactive substance. Immunotherapy is a treatment that can boost the natural defenses of the immune system, but how well it works varies from patient to patient. Recent efforts aim to understand whether blocking unhealthy inflammation with canakinumab and stimulating the body's protective system with immunotherapy at the same time could be an efficacious treatment for patients with lung cancer. Currently there are limited data from experiments in cell and animal models; however, data from the ongoing CANOPY-N clinical trial, which is investigating this treatment combination prior to surgery for patients with lung cancer, are expected by the first half of this year.

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The hallmarks of cancer include sustaining proliferative signaling, evading growth suppressors, activating invasion and metastasis, enabling replicative immortality, inducing angiogenesis and resisting cell death [1]. A key mediator of lung carcinogenesis, dysregulated inflammation, has been described as an enabling characteristic of malignancy, tumor suppressor inactivation and oncogene activation [1–5]. Dysregulated, chronic inflammatory conditions or infections can contribute to tumor initiation and development. Chronic obstructive pulmonary disease, inflammatory bowel disease and chronic hepatitis are associated with higher incidences of lung cancer, colorectal cancer and hepatocellular carcinoma, respectively [6–8].

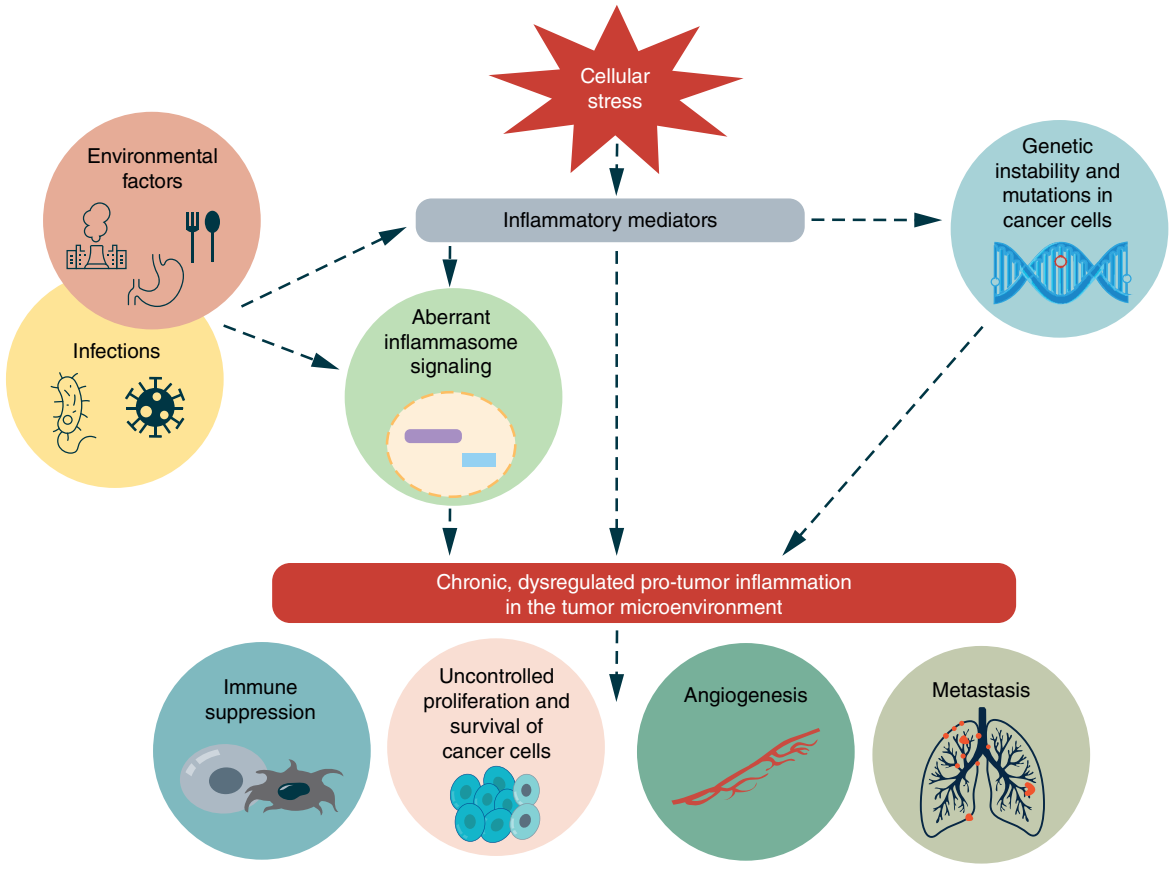


Figure 1. The role of inflammation in tumorigenesis. Several factors can lead to the activation of inflammatory mediators that contribute to the increasing genetic instability and mutagenesis in cancer cells. This, in turn, can enhance the dysregulated protumor inflammation in the tumor microenvironment fueled by inflammatory mediators. This protumor inflammation in the tumor microenvironment causes immunosuppression, facilitates cancer cell survival and proliferation and induces angiogenesis and metastasis.

Protumor inflammation is a characteristic that underpins several of the hallmarks of cancer through multiple mechanisms, such as the production of growth factors, angiogenic factors and extracellular matrix-modifying enzymes that facilitate angiogenesis, invasion and metastasis and the production of reactive oxygen species with mutagenic potential [1,3]. Disruption of the balance between antitumor immune responses, mediated by innate and adaptive immunity and protumor inflammation, can lead to immune escape and tumor growth [9–11]. Here, we review the role of dysregulated, chronic, protumor inflammation in mediating immunosuppression in the tumor microenvironment (TME) and the importance of interleukin (IL)-1β in chronic inflammation and immunosuppression in carcinogenesis. We also examine evidence supporting the rationale for combined IL-1β and immune checkpoint inhibition as a novel therapeutic strategy in non-small-cell lung cancer (NSCLC).

Inflammation & carcinogenesis

Inflammation is critical for tissue repair, regeneration and remodeling, all of which are essential for tissue homeostasis regulation [9]. Chronic inflammation can contribute to the pathogenesis of several diseases, and can promote cancer development at all stages of tumorigenesis (Figure 1) [2,4,9,12]. Cellular stress initiates a cascade of transcription factors and proinflammatory cytokines that drive chronic inflammation via multiprotein complexes called inflammasomes [13–15]. Inflammasomes act as intracellular signaling hubs, whose activation modulates the immune system, promoting or suppressing cancer development; aberrant inflammasome signaling fuels inflammation in the TME and leads to cancer [13,14]. Growing evidence implicates infections and environmental factors such as diet, gut microbiota and inhaled particulates in inflammasome signaling [13,16]. Inflammatory mediators induce genetic instability and accumulation of genetic mutations in cancer cells, leading to atypical signaling and subsequent

chronic inflammation. Although the mechanism is not yet fully understood, one model suggests that IL-1β–mediated induction of mutagenic reactive oxygen species promotes the formation of pre-malignant lesions [17]. IL-1β, via NF-κB, drives expression of protumorigenic genes involved in cell proliferation, differentiation and apoptosis and leads to the accumulation of mutations in premalignant cells [18–20].

Inflammatory cytokines increase the activity of the activation-induced cytidine deaminase enzyme that can contribute to genomic instability and mutations in many types of cancers [21]. IL-1β-driven inflammation induced by commensal microbiota in the lung can also promote development of lung adenocarcinoma [22]. In the TME, dysregulated inflammation is associated with uncontrolled cellular proliferation, apoptosis resistance, cancer cell survival, angiogenesis, metastasis, immune suppression and resistance to therapy [3,5].

Chronic inflammation can modulate the cellular plasticity of cancer, stromal and inflammatory cells within the TME; thereby, facilitating cancer development and progression [3,9]. NF-κB-regulated cytokines controlling the inflammatory milieu act on cancer cells. This activates downstream oncogenic signaling pathways such as ERK, which results in production of inflammatory mediators and activation and recruitment of immune and stromal cells to the TME [9].

The complex interaction of immune cell infiltrates and stromal cells in the TME has dual roles of anti- and protumor functions [9]. Antigen-presenting cells prime the antitumor function of cytotoxic cluster of differentiation (CD)8^+ T cells to detect and eliminate immunogenic tumor cells [15]. Conversely, tumor-associated macrophages (TAMs) trigger inflammatory cytokine production to promote tumor growth [23] and, in later stages of tumor progression, produce immunosuppressive mediators that attenuate antitumor T-cell function [15]. IL-17-producing T cells have a dual role in tumors: they contribute to the initiation of malignant tumors and fibrosis, but cause antitumor regression in late stages of cancer [15].

This evidence collectively supports the concept that immune cell plasticity is influenced heavily by inflammatory mediators and how anti- and protumor properties of cytokines on epithelial, stromal, immune and cancer cells sculpt the TME. The terms 'immunologically hot' or 'inflamed' tumors refer to TMEs with a high influx of T-cell infiltrates and antitumor immune capacity. 'Immunologically cold,' 'immune-desert' or 'non-inflamed' tumors are TMEs lacking antitumor properties, as a result of low levels of T cells [9,15,24]. However, these terms do not consider the essential role of dysregulated, chronic inflammation in creating a tumor-permissive and promoting microenvironment. There is a need to expand our understanding beyond the 'hot' TME, to include 'dysregulated inflammation' or 'protumor inflammation' as a critical process in carcinogenesis and target for therapeutic intervention [9]. Promoting a nonspecific 'hot' TME may in fact facilitate the seeding of metastasizing cancer cells due to remodeling of the extracellular matrix into a tumor-permissive microenvironment [25].

IL-1β role in protumor inflammation

IL-1β

IL-1β is one of 11 members of the IL-1 cytokine family and a major agonist of IL-1 receptor (IL-1R)-1 (Figure 2A) [26–28]. IL-1β signaling recruits an adaptor protein called myeloid differentiation primary response–88 (MyD88) and IL-1R associated kinases [26,27]. This activates the mitogen activated protein kinase pathway and NF-κB, consequently activating downstream inflammatory pathways [26,27]. In response to cellular stress, inflammasomes are assembled (Figure 2B); the nucleotide-binding domain, leucine-rich family, pyrin domain-containing-3 (NLRP3) inflammasome converts the proenzyme procaspase-1 to protease caspase-1. Caspase-1 cleaves the pro-IL-1β precursor, releases active IL-1β and induces pyroptosis, an inflammation-mediated cell death [13,14,26,27]. IL-1β has many targets and subsequent effects in the TME such as immune cells (e.g., myeloid-derived suppressor cells (MDSC), natural killer, $CD8^+$), cancer cells (e.g., epithelial–mesenchymal transition (EMT) phenotype) and inflammatory mediators and cytokines (e.g., IL-6, IL-8, VEGF) (Figure 3).

IL-1β association with cancer

Aberrant IL-1β expression has been associated with lung cancer development, and high expression is associated with worse prognosis. *IL1B* –31C>T gene polymorphisms, CT and TT, are all associated with NSCLC [29]. A meta-analysis of 12 studies identified an association of *IL1B* –31C>T and +3954C>T polymorphisms with an increased risk of lung cancer [30]. IL-1β serum levels in patients with NSCLC were significantly higher compared with healthy controls [31]; this finding was replicated in NSCLC patient subsets of lung adenocarcinoma and lung squamous cell carcinoma (LUSC) [32]. Some studies have demonstrated a role for IL-1β in reflecting prognosis or pathological stage of lung cancer. Wu and colleagues reported an association between IL-1β serum levels and

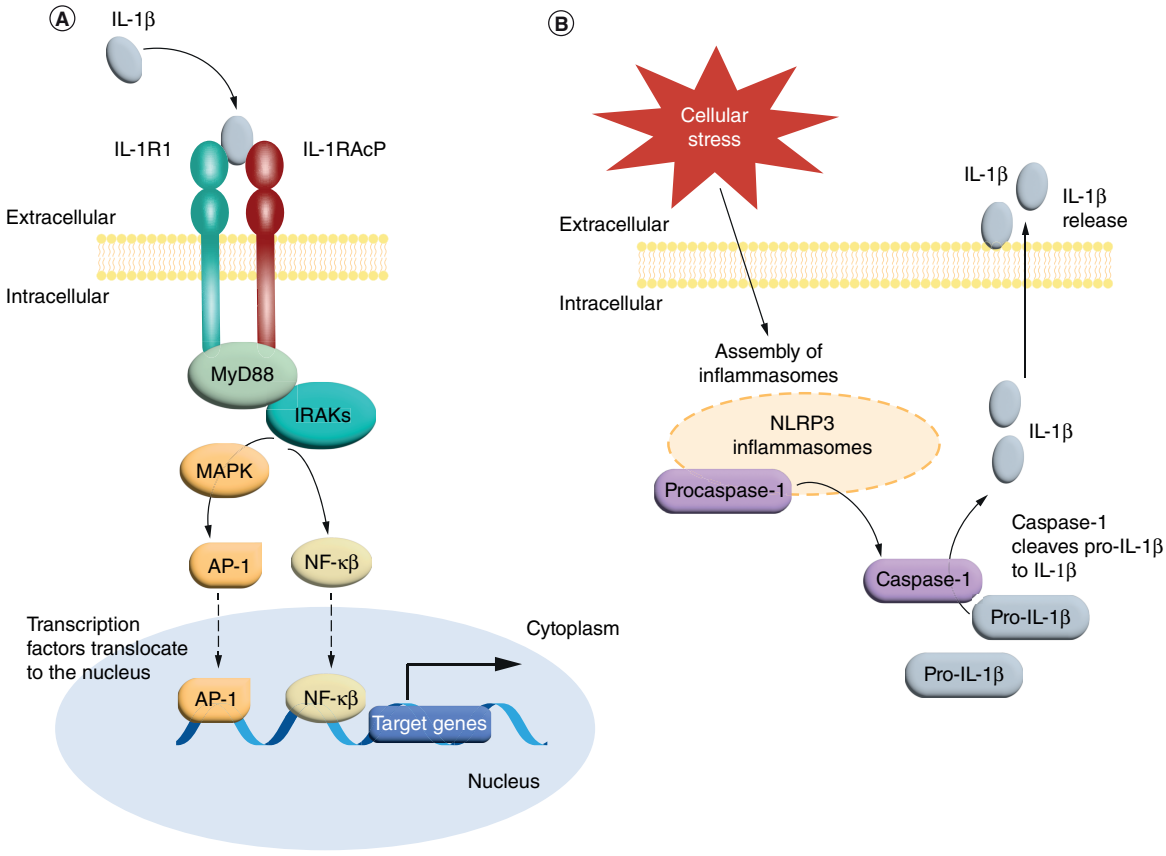


Figure 2. IL-1β signaling in cancer. (A) The signaling pathway and downstream effects of IL-1β. **(B)** The role of the inflammasome in producing IL-1β.
IL: Interleukin; IRAK: Interleukin-1 receptor-associated kinase; MAPK: Mitogen-activated protein kinase; MyD88: Myeloid differentiation primary response–88; NLRP3: Nucleotide-binding domain, leucine-rich family, pyrin domain-containing-3.

pathological stage in patients with LUSC [32]. In another study in patients with surgically treated early-stage NSCLC, increased IL-1β protein levels were significantly associated with poorer prognosis in the adenocarcinoma subtype [33]. Gene expression analysis from The Cancer Genome Atlas and Molecular Taxonomy of Breast Cancer International Consortium databases reported a significant increase in *IL1B* transcript expression in basal breast cancer, a disease with a relatively poor prognosis [34]. *IL1B* gene expression in primary breast cancer biopsies from untreated patients was associated with a significant risk of disease recurrence at any site and bone metastasis [35]. High IL-1β expression or production levels are associated with multiple cancer types [35–38]; however, it should be noted that increased IL-1β signaling has also been associated with infection, such as hepatitis B or Epstein–Barr virus [39,40]. Nevertheless, the evidence collectively proposes a key role for IL-1β in cancer immunopathogenesis.

IL-1β & immunosuppression

Multiple studies have linked IL-1β either directly or indirectly to the activation and recruitment of MDSCs into the TME (Figure 3) [17,41–45]. MDSCs are derived from immature myeloid cells from the bone marrow, which migrate to solid tumors through the circulatory system [46]. MDSCs promote tumor progression by inducing the expansion of $CD4^+$ $CD25^+$ Foxp3+ Tregs in the TME; this, in turn, downregulates the antitumor function of natural killer cells and cytotoxic T cells, resulting in immunosuppression [2,46,47]. Once in the TME, some MDSCs differentiate into immunosuppressive TAMs [46]. The accumulation and retention of MDSCs through the persistence of IL-1β and other mediators in the TME maintain an immune-suppressive state. IL-1β inhibition may be a strategy to abrogate MDSC-directed, Treg mediated immunosuppression.

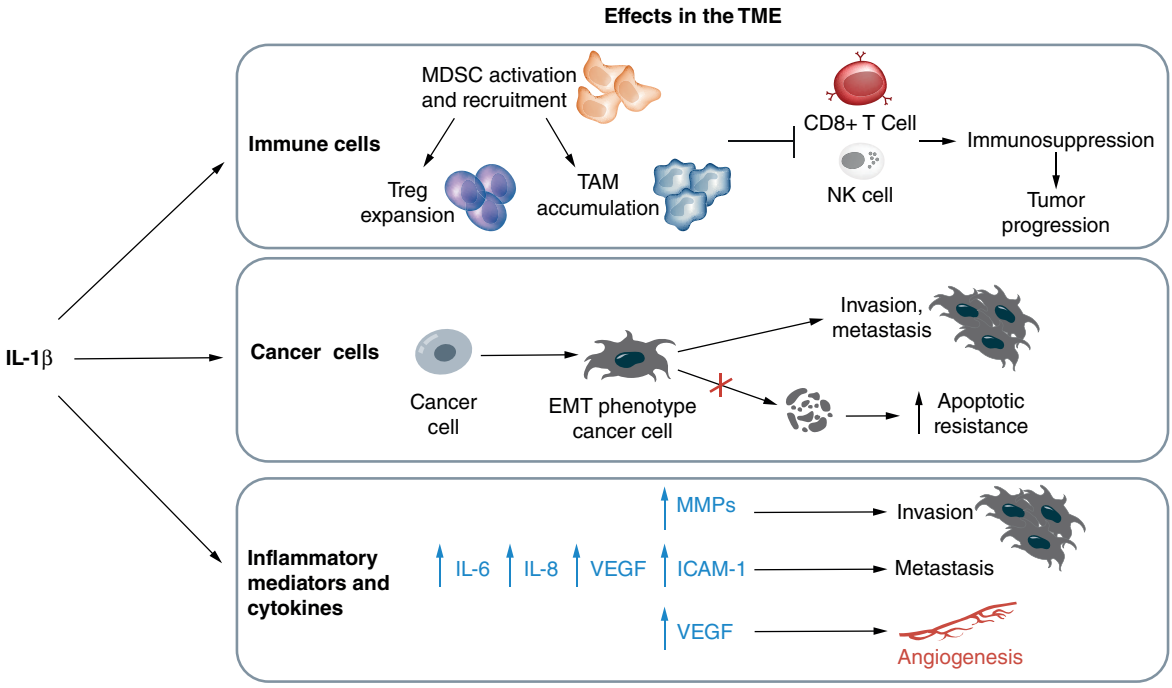


Figure 3. Targets and effects of IL-1β in the tumor microenvironment.
EMT: Epithelial–mesenchymal transition; ICAM-1: Intercellular adhesion molecule-1; IL: Interleukin; MDSC: Myeloid-derived suppressor cell; MMP: Matrix metalloproteinase; NK: Natural killer; TAM: Tumor-associated macrophage; TME: Tumor microenvironment.

IL-1β & tumor invasiveness & metastasis

IL-1β is an important cytokine in the TME that promotes invasiveness and metastasis, providing further rationale to target IL-1β in cancer (Figure 3) [48]. IL-1β is a potent regulator of the cyclooxygenase 2/prostaglandin E_2 pathway, which modulates invasion, EMT, apoptosis resistance and angiogenesis [49]. In a study of lung cancer cell lines, IL-1β promoted metastasis via stimulation of inflammatory mediators, such as IL-6, IL-8, VEGF and intercellular adhesion molecule 1 [50]. In another study, NSCLC A549 cell lines cultured with chronic IL-1β stimulation for 21 days progressed to an EMT phenotype that is associated with cancer metastasis, migratory and invasive functions and apoptotic resistance. The EMT phenotype was sustained for 30 days after IL-1β withdrawal, suggesting a role for IL-1β exposure in EMT memory [51]. As such, EMT may be induced by chronic IL-1β exposure and persists despite elimination of the initial inflammatory trigger [51]. Additionally, spontaneous lung metastases were observed in wild-type mice injected with 4T1 mammary carcinoma cells, but not in IL-1β knockout mice, suggesting a role for IL-1β in lung cancer progression [43]. IL-1β increases cell invasiveness in other cancer types, namely breast cancer [35,43,52,53]. Exogenous recombinant IL-1 has also been shown to induce production of growth and invasiveness-promoting factors [20]. These data together support IL-1 and IL-1β as being involved in controlling tumor growth and invasion.

Interleukin-1β & angiogenesis

The role of IL-1β in angiogenesis is well established (Figure 3). Increasing IL-1β and VEGF levels are associated with increased angiogenesis *in vitro*, as shown with B16 melanoma cells in Matrigel plug invasion assays [42]. In IL-1β knockout mice, decreased numbers of blood vessels, VEGF-producing cells, and α-smooth muscle actin levels were reported, indicating reduced angiogenic response [42]. In mice, the injection of recombinant IL-1β or VEGF led to the production of VEGF and IL-1β, respectively; both induce a potent angiogenic response. The IL-1β–associated angiogenic response was mediated by VEGF and *vice versa*, demonstrating crosstalk between the two angiogenic factors [42].

Targeting IL-1β inhibition in cancer

Based on the evidence implicating IL-1β in carcinogenesis, inhibiting IL-1β may be a promising therapeutic strategy in cancer. Wu *et al.* reported improved prognosis in patients with lung adenocarcinoma or LUSC with low IL-1β levels [32]. In another study, Wu and colleagues described how IL-1β neutralization may prevent breast cancer progression [34]. Humanized mice treated with anakinra the IL-1 receptor antagonist anakinra, reduced the mean breast cancer tumor volume compared with control [34]. IL-1β expression in breast cancer tissues highly correlated with expression of genes associated with IL-1β cleavage via the inflammasome and caspase-1 [34]. Wu and colleagues also reported results from a pilot clinical trial (NCT01802970) in 11 patients with HER2-negative breast cancer receiving anakinra 100 mg once daily for a 2 week run-in period, followed by anakinra with weekly chemotherapy until development of treatment-limiting toxicity or progressive disease [34]. Blood transcriptional analysis of these patients post-treatment demonstrated downregulation of the expression of genes encoding inflammatory cytokines, namely IL-1- and IL-6-related and NF-κB associated genes [34]. IL-1 blockade also upregulated expression of genes encoding cytotoxic function in T cells; therefore, IL-1 inhibition both downregulates inflammation and modifies the genetic signature to restore antitumor immunity in patients with metastatic breast cancer [34].

IL-1β is a protumorigenic mediator which may explain the lack of effectiveness of NF-κB inhibitors as cancer treatments. In genetically altered mice with a myeloid cell-specific deletion of IKKβ, the activator of NF-κB, exposure to the carcinogen urethane led to an increased number of lung tumors as well as lung neutrophils. Elevated neutrophils were also present in wild-type mice exposed to urethane and treated with bortezomib, a proteasome inhibitor which blocks the degradation of the NF-κB inhibitor. This was paired with an increase of IL-1β protein in the lungs. The correlation between systemic NF-κB inhibition and increased plasma IL-1β levels was confirmed in a study of 28 chemotherapy-naive patients with advanced (stage III–IV) NSCLC, who received one cycle of bortezomib followed by standard chemotherapy or combination therapy (NCT01633645) [54]. Treatment with bortezomib significantly increased IL-1β protein levels; IL-1β levels at baseline were significantly correlated with reduced progression-free survival. Since IL-1β production was increased in tumor models with NF-κB inhibition, McLoed and colleagues investigated how blocking the IL-1 pathway in combination with bortezomib would affect tumor growth. The addition of anakinra with bortezomib in murine lung cancer models significantly reduced tumor growth compared with with anakinra or bortezomib alone. Bortezomib monotherapy has been shown to be ineffective as a single agent for first-line treatment of NSCLC [55]. These studies support a causative role for neutrophil-derived IL-1β in lung tumorigenesis and demonstrate that the addition of IL-1R antagonist to NF-κB inhibition may improve the effectiveness of NF-κB inhibitor therapy; future clinical trials of anti-IL-1 inhibition and bortezomib in NSCLC are warranted.

Another study demonstrated that the chemotherapy agents gemcitabine and 5-fluorouracil (5-FU) induced IL-1β production by EL4 tumor-bearing mice via inflammasome activation in MDSCs [56]. The antitumor effects of 5-FU were increased in the absence of *Nlrp3* and *Casp1* genes, and were further enhanced with the combination of anakinra. This suggests that IL-1 restrains the effects of 5-FU and therefore, the inhibition of IL-1 in combination with 5-FU may enhance antitumor function. These studies suggest that combination strategies with IL-1β inhibition may overcome resistance mechanisms to other therapeutic drugs.

Rationale for combined IL-1β & programmed cell death protein-1 inhibition in cancer

Preclinical data supporting combined targeting of IL-1β & PD-1 in cancer

The relationship between programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1) and IL-1β in humans is poorly understood. IL-1β is a potent proinflammatory cytokine produced by cells of the innate immune system and PD-L1 is a critical suppressive protein that plays a key role in innate (e.g., natural killer cells, macrophages and dendritic cells) and adaptive (B and T cells) immune responses and is also expressed by tumor cells [57–60]. Resected tumor samples from patients with early-stage lung adenocarcinoma showed an association between IL-1β and IL-6 expression and PD-1 expression, suggesting a possible interaction between these mediators [61]. In another study, PD-L1 expression correlated with IL-1β expression in HCC tissues [62]. IL-1β receptor knockdown inhibited PD-L1 expression in M1 macrophages; although, recombinant IL-1β induced PD-L1 expression in HCC cells [62]. This may suggest a positive feedback mechanism between these molecules, which may contribute to their synergistic effects in cancer. However, further investigation is required.

Kaplanov and colleagues reported pivotal preclinical murine data on the use of anti-IL-1β and anti-PD-1 combination therapy. Lung metastases were observed in wild-type mice injected with 4T1 mammary carcinoma cells at 25 days, but not in IL-1β knockout mice, demonstrating a role of IL-1β in lung cancer [43]. This study

was extended to investigate the effects of combined IL-1β and PD-1 inhibition on tumor growth. At days 4 and 7, 4T1-injected BALB/c mice were treated with anti-IL-1β neutralizing antibodies to reduce IL-1β-mediated immunosuppression. Mice were treated with anti-PD-1 neutralizing antibodies at day 10 to activate anergized antitumor T cells, which are in a hyporesponsive state with incomplete activation and increase their recruitment to the TME. Inhibition of either IL-1β or PD-1 alone only partially reduced tumor growth; combined IL-1β and PD-1 inhibition synergistically and significantly inhibited tumor growth for 30 days and increased tumor infiltrating $CD8^+$ T-cell frequencies compared with the control [43]. IL-1β neutralization reduced myeloid cell recruitment and maturation of immunosuppressive macrophages; whereas, PD-1 inhibition increased the frequency of infiltrating $CD8^+$ T cells, restoring their antitumor function from their previous anergized state [43].

The relationship between IL-1β and PD-L1 expression levels is not fully understood. Among the mechanisms by which tumor cells evade immune surveillance is expression of immune checkpoint inhibitors ligands such as PD-L1 and facilitation of $CD8^+$ T cell exhaustion, leading to the suppression of the antitumor immune response [63]. Existing preclinical evidence in various solid tumor-derived cancer cells suggests that targeting IL-1β leads to decreased PD-L1 expression. Upregulation by IL-1 of COX-2 and PD-(L)1 in melanoma patient derived tumor associated fibroblasts was shown to be partially responsible for the inhibition of cytotoxic T-cell function [64]. In a recent study by Li *et al.*, it was demonstrated that chronic IL-1β induced inflammation regulates epithelial-to-mesenchymal phenotypes via epigenetic modifications in NSCLC [65]. Preclinical evidence in established mouse models of pancreatic ductal adenocarcinoma has shown that antibody-mediated neutralization of IL-1β significantly enhanced the antitumor activity of anti-PD-1 and was accompanied by increased tumor infiltration of $CD8^+$ T cells [66]. The protumor role of IL-1β in pancreatic ductal adenocarcinoma via B lymphocyte-mediated immune suppression was recently demonstrated in a study where B cells isolated from KRAS-mutant mice overexpressing IL-1β had much higher expression levels of PD-L1, more regulatory B cells, impaired $CD8^+$ T-cell activation and promotion of tumorigenesis [67]. Inhibition of malignant tumor growth in IL-1β deficient mice and loss of the immunosuppressive effect by depletion of $CD8^+$ T cells and blockade of lymphocyte mobilization have been reported recently [68].

The role of IL-1β as an important mediator of intratumoral immunosuppression is supported by another study which investigated whether combining IL-1β inhibitors with anti-PD-1 or the multikinase inhibitor cabozantinib could delay tumor growth though modulation of the myeloid compartment of the TME in a murine model for renal cell carcinoma (RCC). Mice were treated on day 12 with cabozantinib, anti-PD-1, anti-IL-1β and either anti-PD-1 in combination with anti-IL-1β or cabozantinib in combination with anti-IL-1β [69]. Compared with vehicle, tumor weights on day 18 were significantly reduced with anti-IL-1β or anti-PD-1 monotherapy [69]. However, the largest reduction in tumor weight was achieved with anti-IL-1β in combination with anti-PD-1 [69]. Compared with anti-IL-1β monotherapy, the addition of anti-PD-1 led to a significant decrease in tumor weight [69]. Combined anti-IL-1β and anti-PD-1 decreased polymorphonuclear MDSC infiltration to a greater degree than anti-PD-1 monotherapy and increased the frequency of M1-like TAMs [69]. This was also noted with anti-IL-1β monotherapy, suggesting that IL-1β inhibition may block the expansion or recruitment of immunosuppressive MDSCs to the TME [69]. Anti-IL-1β combined with either anti-PD-1 or cabozantinib led to a more significant reduction in tumor growth than either agent alone [69].

Both *in vivo* preclinical murine studies support the rationale to target dysregulated pro-tumor inflammation with combined anti-IL-1β and anti-PD-1 therapy. IL-1β blockade targets the innate early response and reduces dysregulated inflammatory cytokine release; whereas, PD-1 blockade targets the antitumor immunity of anergized T cells [43,70].

Recent studies have highlighted the crosstalk between inflammasomes and PD-(L)1. Further research is needed to understand how these two pathways are mutually dependent and why targeting a single pathway may be ineffective in some patients. For example, in a recent study in patients with asymptomatic multiple myeloma, inhibition of the PD-L1 was correlated with increased IL-1β production, in support of the crosstalk between the two pathways [71]. Combination therapy targeting both innate and adaptive responses may be advantageous in treating both early- and late-stage lung cancer.

IL-1β inhibition in clinical trials in lung cancer

Clinical inhibition of IL-1β by the high-affinity and specific human monoclonal antibody canakinumab in lung cancer was first reported in an exploratory analysis of the phase III Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS; NCT01327846) [72–74]. This randomized trial involved 10,061 patients with

atherosclerosis and myocardial infarction; the canakinumab cohort demonstrated significantly lower incidences of nonfatal and fatal lung cancer, as well as overall lung cancer mortality, compared with placebo for those patients with a high-sensitivity C-reactive protein (CRP) level ≥2 mg/l (Figure 4) [72,73]. The impact of canakinumab on lung cancer incidence was dose-dependent (50, 150 and 300 mg cohorts), with the greatest effect in the 300 mg group (Figure 4) [72].

Although this was not its primary objective, CANTOS was the first study to demonstrate significantly lower incidences of lung cancer with canakinumab, providing the rationale for evaluating canakinumab in lung cancer [72]. The CANOPY program (comprising CANOPY-A, CANOPY-1, CANOPY-2 and CANOPY-N) was consequently developed to assess the efficacy of targeting IL-1β in different settings for the treatment of patients with NSCLC [75].

CANOPY-A (NCT03447769) aims to evaluate adjuvant canakinumab 200 mg subcutaneously (sc.) every 3 weeks (Q3W) versus placebo in 1500 patients with stage IIA–IIIA and IIIB completely resected NSCLC [75,76]. Disease free survival is the primary end point [75]. CANOPY-2 (NCT03626545) aimed to assess canakinumab 200 mg sc. Q3W with docetaxel versus placebo with docetaxel in 226 patients with stage IIIB–IV NSCLC who had been previously treated with PD-L1 inhibitors and chemotherapy [75]. The primary end point of overall survival was not met [75,77]. CANOPY-1 and CANOPY-N, which investigate IL-1β and PD-1 inhibition, will be discussed in more detail in the next section.

Combined IL-1β & PD-1 inhibition in clinical trials in lung cancer

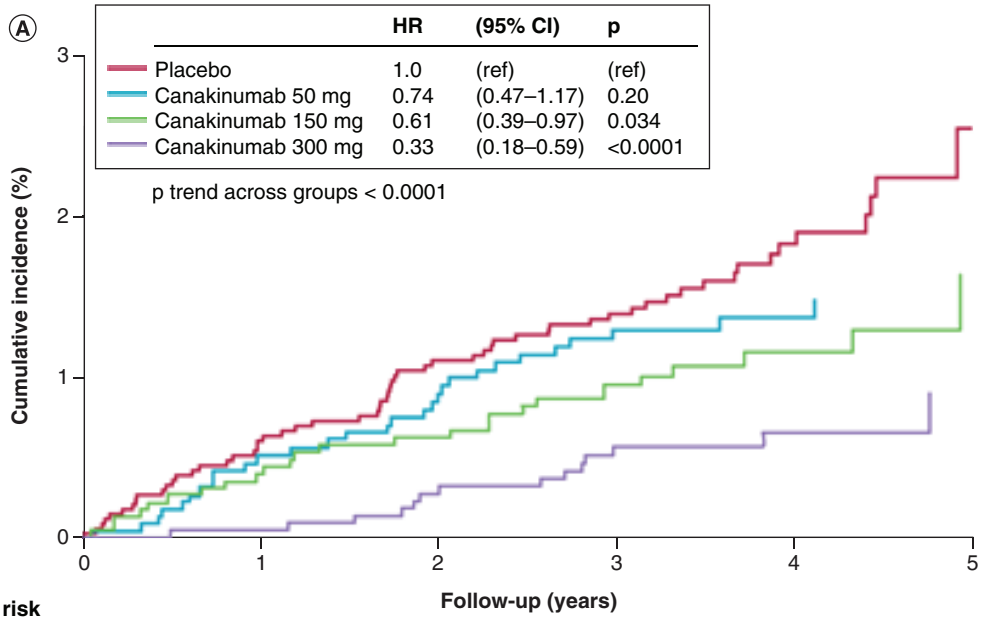
Two clinical trials in the CANOPY program were designed to evaluate combined IL-1β and PD-1 inhibition to treat patients with NSCLC. CANOPY-1 (NCT03631199) is a phase III trial aimed to assess pembrolizumab plus platinum-based doublet chemotherapy with or without canakinumab as first-line treatment in previously untreated stage IIIB/IIIC–IV non squamous and squamous NSCLC [78]. The ongoing CANOPY-N (NCT03968419) phase II study aims to evaluate either canakinumab or the PD-1 inhibitor pembrolizumab as monotherapy or in combination as neoadjuvant treatment in resectable, stage IB-IIIA NSCLC [79].

In the safety run-in part of the CANOPY-1 trial (n = 30), patients received canakinumab 200 mg sc. Q3W with pembrolizumab 200 mg iv. Q3W with either: carboplatin and pemetrexed (nonsquamous); cisplatin and pemetrexed (nonsquamous); or carboplatin and paclitaxel (squamous or nonsquamous) [80]. Serious adverse events (AEs) were reported in eight (27%) patients and AEs leading to discontinuation of one of the study drugs were reported in three (10%) patients; these were unrelated to canakinumab. No fatal serious AEs were reported, and one dose-limiting toxicity during the first 42 days of study treatment was reported with canakinumab in combination with pembrolizumab and chemotherapy. The recommended phase III regimen of canakinumab was confirmed as 200 mg sc. Q3W with standard dose of pembrolizumab and chemotherapy and considered safe and well tolerated. These data show no new safety concerns. In a recent press release, it was announced that CANOPY-1 did not meet its primary end points. However, the data suggest that some patient subgroups may benefit from canakinumab treatment and additional biomarker driven analyses to identify those patients are ongoing [78,80,81].

CANOPY-N is ongoing at the time of writing [82]. Surgical resection will be performed approximately 4–6 weeks from study drug administration (either canakinumab or pembrolizumab as monotherapy or a combination of the two) [79]. The primary end point of CANOPY-N will determine the major pathologic response rate (MPR; defined as ≤10% viable tumor in resected specimen) based on central review, and secondary end points will investigate overall response rate, surgical feasibility rates, antidrug antibodies incidence, pharmacokinetic parameters, MPR based on local review and MPR based on biomarker level. The CANOPY-N study of the inhibition of both IL-1β and PD-1 is intended to validate preclinical data and assess whether there is a synergistic improvement in efficacy and safety in patients with NSCLC [79].

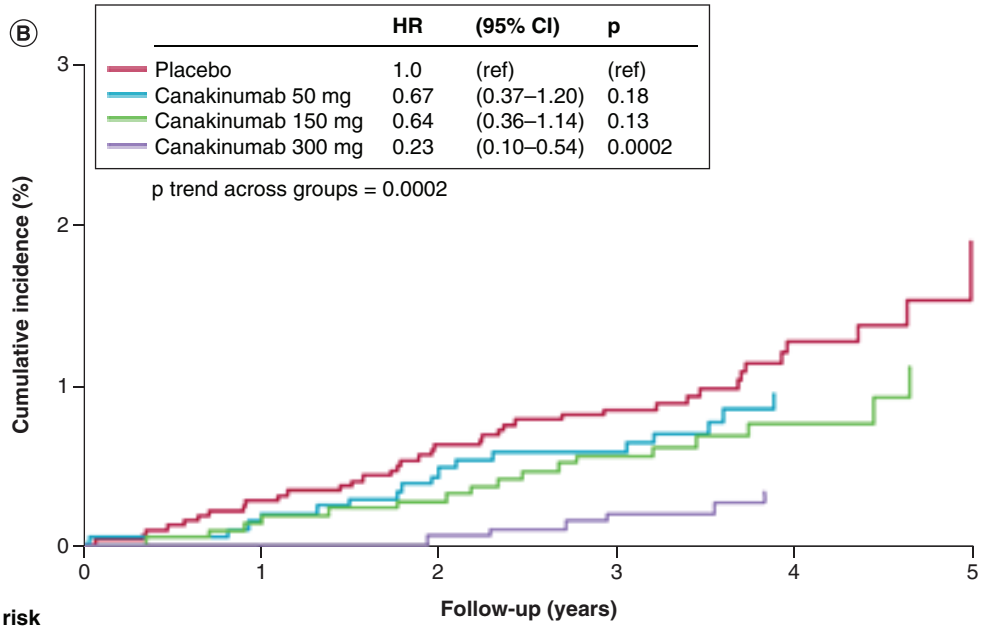
To best of the authors' knowledge, there are two trials of IL-1 inhibitors in solid tumors: one in combination with an immune check point inhibitor and one as monotherapy [83,84]. At the time of writing, an investigator-initiated phase I/IIA, non randomized, open-label dose escalation and expansion trial with isunakinra (IL-1α/β inhibitor) alone and in combination with anti-PD-(L)1 in patients with metastatic or unresectable, locally advanced malignant solid tumors is recruiting [83]. A National Cancer Institute (NCI) sponsored phase I study of anakinra monotherapy mediated tumor regression and angiogenesis inhibition in patients with cancers producing IL-1 completed in 2015 but no results have been reported to date [84].

At present, there are two US FDA approved immune checkpoint inhibitors (ICI) regimens in early-stage NSCLC (eNSCLC). In the IMpower010 trial, administration of adjuvant atezolizumab (PD-L1 inhibitor) for 1 year to patients with stage II or III NSCLC and PD-L1 expression ≥1% following complete resection and platinum based



Number at risk

Placebo	3344	3241	3142	2835	1401	251
Canakinumab 50 mg	2170	2110	2047	1825	827	53
Canakinumab 150 mg	2284	2207	2148	1950	982	233
Canakinumab 300 mg	2263	2201	2128	1928	1002	222



Number at risk

Placebo	3344	3255	3162	2868	1423	257
Canakinumab 50 mg	2170	2117	2054	1845	838	57
Canakinumab 150 mg	2284	2221	2163	1972	998	243
Canakinumab 300 mg	2263	2204	2139	1949	1013	227

Figure 4. Cumulative incidence of lung cancer and fatal lung cancer in the CANTOS trial in patients with atherosclerosis. The incidence rates of **(A)** lung cancer and **(B)** lung cancer mortality were lower in the canakinumab arms compared with the group receiving placebo; lung cancer and lung cancer mortality were significantly less common in the canakinumab 300 mg group than in the placebo group.
HR: Hazard ratio.
Figure reused with permission from the publisher [72].

chemotherapy showed significant disease-free survival advantage compared with best supportive care (Hazard radio [HR]: 0.66, 95% CI: 0.50–0.88) [85]. In contrast, in the CheckMate 816 trial, neoadjuvant nivolumab plus platinum doublet chemotherapy for three cycles administered to patients with stage IB–IIIA NSCLC, regardless of *PD-L1* expression, showed a significant event free survival advantage compared with chemotherapy alone (HR: 0.63; 97.38% CI: 0.43–0.91) [86].

Based on these findings, ICI has clearly established its role as standard of care in eNSCLC. However, several controversies exist. The most effective ICI regimen (chemotherapy-free combination immunotherapy or combined ICI plus chemotherapy) and timing of administration (neoadjuvant, adjuvant or both) are unclear. At present, there is no approved chemotherapy free approved ICI regimen in eNSCLC. Clinically, a chemotherapy-free regimen is most needed for patients with poor performance status, elderly people and contraindications or refusal to chemotherapy. Based on the National Cancer Database (NCDB), in patients >70 years old, the mortality within the first 6 months of starting adjuvant chemotherapy following lung cancer resection is higher, comorbidity scores are higher and postoperative length of stay in hospital is prolonged compared with younger patients [87]. In spite of standard of care recommendation guidelines to administer chemotherapy in patients with stages II–III NSCLC, recent SEERS database analysis showed that 31, 18 and 38% of patients with stages II, IIIA and IIIB eNSCLC, respectively, underwent surgery alone without receiving preoperative or postoperative chemotherapy [88]. As such, there is a substantial portion of patients with eNSCLC who do not receive perioperative chemotherapy. Preoperative immunotherapy strategies such as combined IL-β and PD-1 inhibition (CANOPY-N trial) seek to address this unmet need and may improve ICI efficacy.

Proposed inflammatory biomarkers & outcomes to assess in clinical trials

Given the role of chronic inflammation in lung carcinogenesis, inflammatory biomarker measurement may have the potential to measure response to IL-1β and PD-1 inhibition in clinical trials. This has been studied in other tumor types, for example, carcinoembryonic antigen is a biomarker with diagnostic and prognostic value in colorectal cancer. One study analyzed tumor and paired normal tissue samples from 22 patients who underwent surgery for colorectal tumors. A total of 39 inflammatory molecules, plus CRA and CA19-9 were assessed; a correlation between IL-8, IL-1β and carcinoembryonic antigen was found [89].

CRP is an acute-phase inflammatory protein detected in patients with inflammatory conditions, infections or cardiovascular disease and is induced by the inflammatory cytokine, IL-6 [90]. In a cohort study of 160,000 patients diagnosed with cancer, inflammatory marker CRP, erythrocyte sedimentation rate and plasma viscosity were evaluated [91]. Patients with elevated inflammatory markers had a 1 year cancer incidence of 3.53% (vs 1.50% in those with normal inflammatory markers) [91]. Notably, inflammatory biomarkers have poor sensitivity and cannot be used to rule-out cancer, as 44–50% of tested patients with cancer have normal inflammatory marker test results in the 1st year before diagnosis [91]. In the prostate, lung, colorectal and ovarian cancer screening trial (NCT00002540), increased circulating IL-6 and IL-8 levels were associated with lung cancer; high levels of serum IL-8 and CRP were predictive of increased lung cancer risk [92]. In a case–control study of 592 patients with lung cancer, elevated CRP was associated with increased lung cancer risk among former and current smokers [93]. In a small study of 24 patients with NSCLC compared with 13 healthy controls, serum CRP levels were significantly increased in patients with metastatic NSCLC compared with healthy controls and patients with localized NSCLC [94]. Additionally, elevated baseline CRP was associated with lower odds of response to ICI therapy. Based on a longitudinal CRP trajectory analysis, early CRP decline emerged as a strong predictor of favorable outcome, whereas elevated CRP trajectories were associated with higher progression risk [95,96]. Because IL-1β is known to induce the production of CRP, it could be hypothesized that blocking IL-1β may inhibit protumor inflammation thus slowing tumor progression.

In the CANTOS trial, baseline concentrations of CRP and IL-6 were significantly higher among participants diagnosed with lung cancer than those without a cancer diagnosis. Furthermore, canakinumab demonstrated dose-dependent reductions in high-sensitivity CRP (26–41%) and IL-6 (25–43%) [72]. Patients who achieved greater CRP reductions within the first 3 months of treatment appeared to gain the most benefit from canakinumab. In patients with CRP levels below the median, a 71% reduction in the cumulative incidence of lung cancer was observed; there was no significant benefit for patients with higher CRP levels [97,98]. These findings suggest that inflammatory biomarkers, namely serum CRP or IL-6, may be promising predictive biomarkers in IL-1β suppression treatment strategies, whereby elevated baseline levels may predict responsiveness with expectant reduction in concentration with IL-1β inhibition.

Conclusion

Dysregulated, chronic inflammation has a critical role in lung carcinogenesis, by downregulating tumor suppressors and activating oncogenes. Cellular stress activates transcription factors and cytokines to drive chronic inflammation via inflammasomes and IL-1β. There is a need to expand our understanding beyond the concept of 'hot' or 'cold' tumors to include 'dysregulated inflammation' or 'protumor inflammation' as a critical process in carcinogenesis and target for therapeutic intervention in order to improve specific antitumor immune responses. Growing evidence highlights the role of IL-1β in lung cancer development, supporting IL-1β inhibition as a promising therapeutic target in cancer. Most notably, the impact of clinical IL-1β inhibition with canakinumab in lung cancer was first reported in the phase III CANTOS trial, where the canakinumab cohort of patients with atherosclerosis demonstrated significantly lower incidences of nonfatal and fatal lung cancer compared with placebo.

Two clinical trials in the CANOPY program are evaluating the efficacy of combined IL-1β and PD-1 inhibition to treat NSCLC. Data are also emerging to suggest that inflammatory biomarkers, such as serum CRP or IL-6 levels, may be promising predictive biomarkers in IL-1β suppression treatment strategies. In eNSCLC, a significant percentage of patients with resectable NSCLC do not receive neoadjuvant or adjuvant chemotherapy. The currently approved ICI regimens require either neoadjuvant ICI plus chemotherapy or adjuvant ICI following complete resection and chemotherapy. Therefore, patients with eNSCLC who cannot receive perioperative chemotherapy represent of population subgroup of high unmet need for treatment. The combination of IL-1β and PD-1 inhibition may offer a preoperative immunotherapy regimen that is chemotherapy free, which has the potential to improve ICI efficacy.

In conclusion, combined IL-1β and checkpoint inhibition is a novel strategy which aims to overcome immunosuppression and protumor inflammation in lung cancer. This therapeutic approach may improve the efficacy of checkpoint inhibitors and allow extension of checkpoint inhibition to patient populations that otherwise would have predictably less or no responsiveness to PD-1 inhibition alone.

Future perspective

Protumor inflammation enables tumor development by driving carcinogenic processes and suppressing antitumor immune responses. It is also one of the hallmarks of cancer and potential target in NSCLC. However, more clinical evidence is necessary to support targeting IL-1β in patients with NSCLC. The ongoing canakinumab CANOPY-1 and CANOPY-N trials will further elucidate the potential benefits of combining IL-1β with PD-1 inhibition and provide insights about potential predictive biomarkers in early-stage lung cancer settings.

Executive summary

Inflammation & carcinogenesis

- Chronic, dysregulated inflammation plays a key role in the tumor microenvironment, but clinical data are limited.

IL-1β in carcinogenesis

- Preclinical evidence and early clinical data support targeting the inflammatory cytokine IL-1β as a valid treatment approach in non-small-cell lung cancer.

Rationale for combined IL-1β & programmed cell death protein-1 in cancer

- The combined targeting of IL-1β and programmed death 1 (PD-1) may reduce dysregulated inflammation and promote specific antitumor immunity. The potential for this combination strategy may be greater in the early-stage setting, when tumor burden is lower and protumor inflammation plays a bigger role.

Proposed inflammatory biomarkers & outcomes to assess in clinical trials

- It is important to identify inflammatory biomarkers to guide the selection of patient subgroups who might benefit from IL-1β inhibition.

Financial & competing interests disclosure

JM Lee: is a member of steering or executive committees for clinical trials with AstraZeneca, Genentech and Novartis and reports receiving grants and consulting fees from AstraZeneca, Bristol Myers Squibb, Genentech and Novartis, support for attending meetings from Genentech and AstraZeneca and support with medical writing from Genentech and Novartis; ES Kim: reports receiving personal consulting fees from AstraZeneca, Boehringer Ingelheim and Roche. TSK Mok: is a member of boards of directors for AstraZeneca, Aurora Tele-Oncology Ltd, Hutchison Chi-Med, Lunit USA Inc. and Sanomics Ltd., reports receiving research funding from AstraZeneca, Bristol Myers Squibb, F. Hoffmann-La Roche Ltd., G1 Therapeutics, Merck Serono, Merck

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