New frontiers in NSCLC immunotherapy

NSCLC, non-small cell lung carcinoma.

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Assessing the future of immunotherapy in lung cancer

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Anti-tumour immunity[1–3]

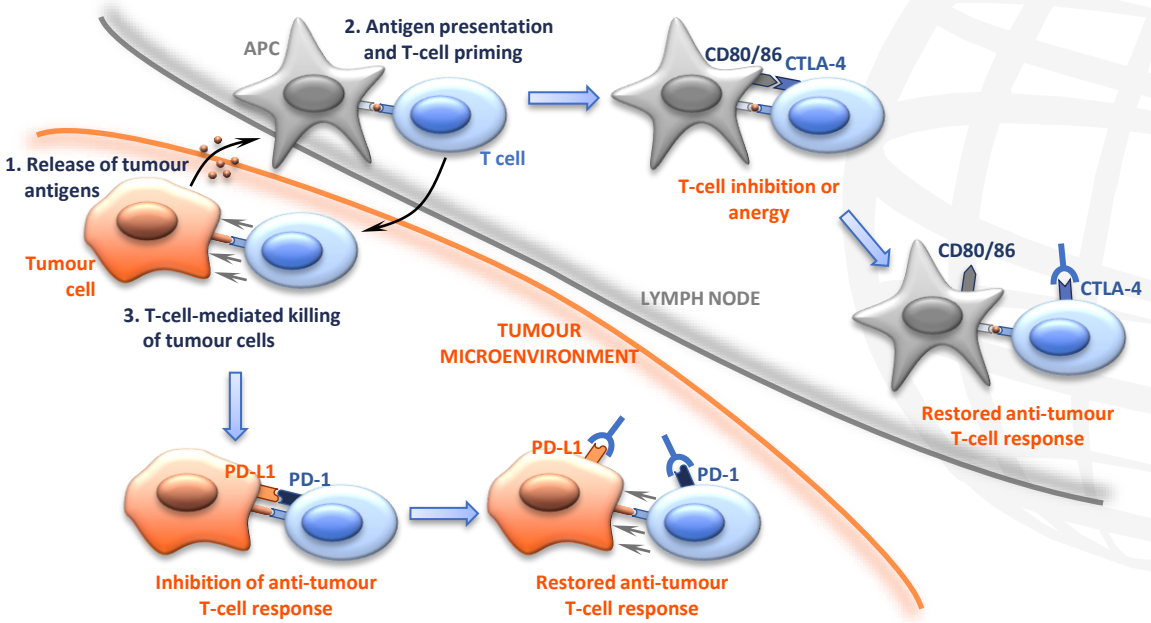
PD-L1, PD-1 and CTLA-4

- PD-1 and CTLA-4 are immunoregulatory receptors expressed on T lymphocytes
- Engagement of CTLA-4 by CD80/86 and of PD-1 by PD-L1 suppress T-cell responses to prevent immune-mediated tissue damage

! The PD-1/PD-L1 and CTLA-4 pathways contribute to tumour immune escape and can be targeted by immunotherapy

Target	Drugs
PD-1	Nivolumab, pembrolizumab, cemiplimab
PD-L1	Atezolizumab, avelumab, durvalumab
CTLA-4	Ipilimumab

Tumour immune escape and checkpoint inhibitors



APC, antigen-presenting cell; CD, cluster of differentiation; CTLA-4, cytotoxic T lymphocyte antigen-4; PD-1, programmed death-1; PD-L1, programmed death-ligand-1.

1. Kim HC, et al. *Tuberc Respir Dis*. 2020;83:14–9; 2. Seidel JA, et al. *Front Oncol*. 2018;8:1–14; 3. Katoh M. *J Thorac Dis*. 2018;10:5178–83.

Use of checkpoint inhibitors in the treatment of advanced (stage 4) NSCLC[1,2]

PD-L1

≥50%

Treatment options

- **Pembrolizumab monotherapy**
  - Preferred to avoid chemotherapy
- **Pembrolizumab + chemotherapy**
- **Nivolumab + ipilimumab**
  - Novel option (not EMA-approved)

<50%

Treatment options

- **Pemetrexed + platinum-based chemotherapy + pembrolizumab**
- **Paclitaxel and carboplatin (carbotaxol) + bevacizumab + atezolizumab**
  - Not EMA-approved
- **Nivolumab + ipilimumab**
  - Not EMA-approved

CTLA-4, cytotoxic T lymphocyte antigen-4; EMA, European medicines agency; NSCLC, non-small-cell lung carcinoma; PD-1, programmed death-1; PD-L1, programmed death-ligand-1.

1. Planchard D, et al. *Ann Oncol*. 2018;29(Suppl. 4):iv192–237; 2. Akamatsu H, et al. *Int J Clin Oncol*. 2019;24:731–70.

Limitations of current immunotherapeutic approaches for advanced stage NSCLC

Unreliable predictive biomarker

Atezolizumab
(BIRCH - NCT02031458)[1]
Treatment-naïve patients
- OS=23.5 months (total)
- OS=26.9 months (PD-L1>50%)

Nivolumab plus ipilimumab
(Checkmate227 - NCT02477826)[2]
- Nivolumab + ipilimumab: OS=17.1 months
- Chemotherapy: OS=13.9 months

Resistance to PD-L1/PD-1 blockade

Multiple mechanisms of primary or acquired resistance[3,4]
- Low antigen levels or lack of antigen presentation
- Other immune checkpoints
- Immune suppressive cells

NSCLC, non-small-cell lung carcinoma; OS, overall survival; PD-L1, programmed death-ligand-1.

1. Peters S, et al. *J Clin Oncol*. 2017;35:2781–9; 2. Hellmann MD, et al. *N Engl J Med*. 2019;381:2020–31; 3. Sharma P, et al. *Cell*. 2017;168:707–23; 4. Chocarro de Erauso L, et al. *Front Pharmacol*. 2020;11:1–13.

The future of immunotherapy for NSCLC

Use of checkpoint inhibitors for NSCLC in earlier disease stages[1]

- Ongoing clinical trials for adjuvant anti-PD-1/PD-L1 in resected stage IB–IIIA NSCLC as a maintenance after adjuvant chemotherapy, either alone or combined with radiotherapy

Molecular targets other than immune checkpoints[2,3]

- Adenosine pathway
- Angiogenesis pathways
- Trp–kyn–aryl hydrocarbon receptor pathway
- PI3K/AKT/mTOR pathway
- Tumour-associated macrophages
- Inflammatory mediators (IL-1)

AKT, protein kinase B; IL-1, interleukin-1; mTOR, mammalian target of rapamycin; NSCLC, non-small-cell lung carcinoma; PD-1, programmed death-1; PD-L1, programmed death-ligand-1; PI3K, phosphoinositide 3-kinases.

1. Indini A, et al. *J Thorac Dis*. 2020;12:3390–8; 2. Giannone G, et al. *Int J Mol Sci*. 2020;21:1–22; 3. Gottschlich A, et al. *Transl Lung Cancer Res*. 2018;7:S160–4.

Untapped potential in the tumour microenvironment

Prof. Sebastian Kobold

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Experimental Immunooncology,
Ludwig-Maximilians-University of Munich,
Munich, Germany

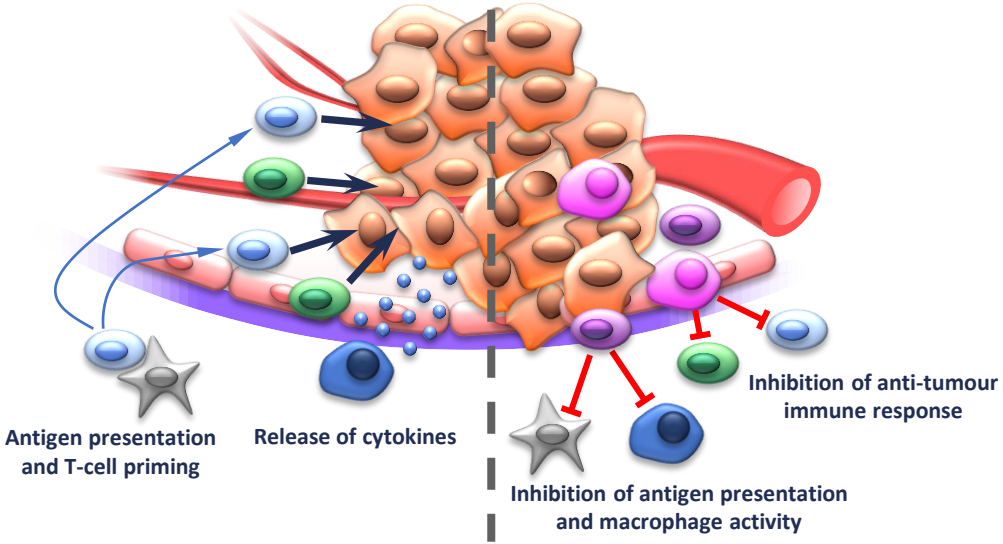
The tumour microenvironment[1–4]

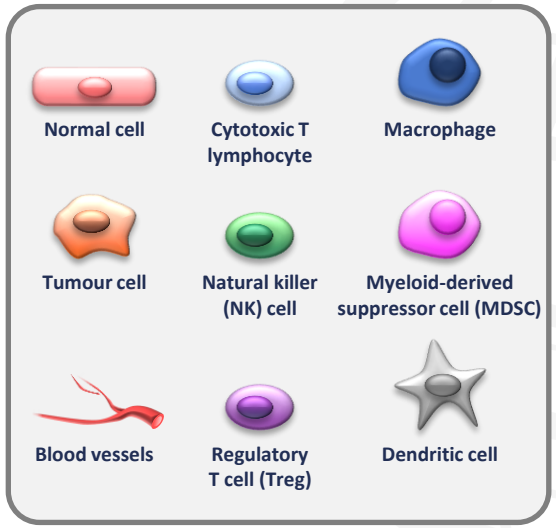
Anti-tumour immune response

Under physiological conditions, immune cells within the microenvironment limit the establishment of the primary tumour

Immune evasion

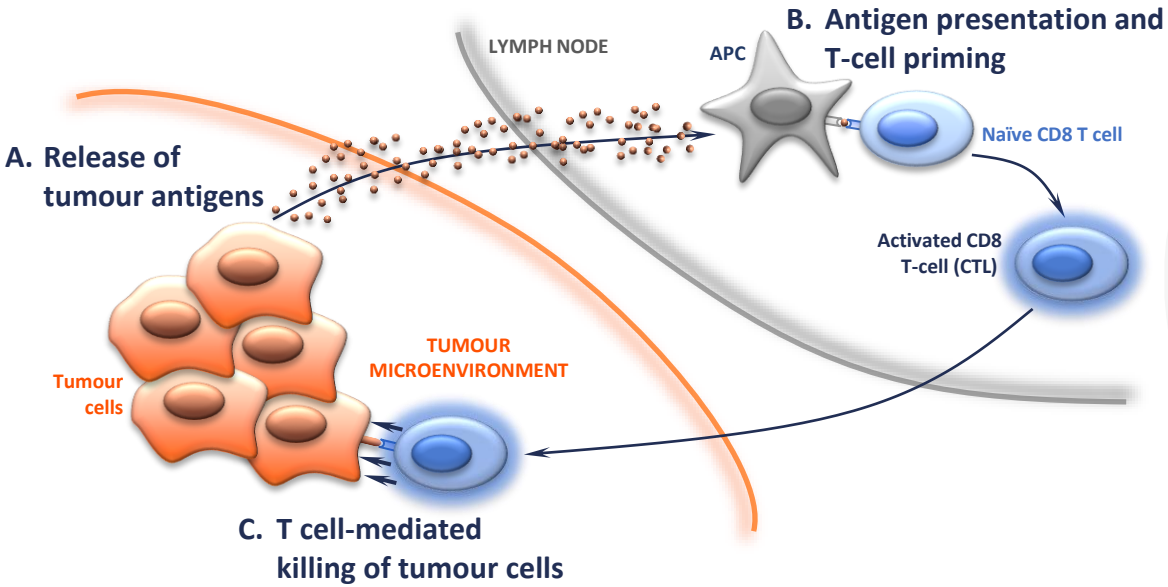
During tumour progression, changes in the local milieu affect the phenotype of surrounding cells, which inhibit effective immune responses against the tumour





1. Quail DF, Joyce JA. *Nat Rev Cancer*. 2017:Poster; 2. Quail DF, Joyce JA. *Nat Med*. 2013;19:1423–37; 3. Maher J, et al. *Br J Cancer*. 2004;91:817–21; 4. Zhang C, et al. *Front Immunol*. 2020;11:1–20.

The tumour immune cycle[1,2]



APC, antigen-presenting cell; CD, cluster of differentiation; CTL, cytotoxic T lymphocyte.

1. Kim HC, Choi C-M. *Tuberc Respir Dis*. 2020;83:14–9; 2. Pio R, et al. *Front. Immunol*. 2019;10:774.

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Immunotherapy targets within the tumour immune cycle

PD-1/PD-L1

Tumour cells upregulate PD-L1 in response to IFN-γ. PD-L1 binding to PD-1 on T cells causes T-cell apoptosis, anergy and exhaustion.[1–3]

CTLA-4

CTLA-4 is expressed by Tregs and can be upregulated by T cells. CTLA-4 dampens immune responses against infections and tumours.[3]

LAG-3

LAG-3 is expressed on both Treg and anergic CD4 T helper cells. LAG-3 binds MHC class II and inhibits CD4 T-cell activation.[4]

IL-1β

Overexpression of IL-1β increases inflammation-associated tumour invasiveness and favours cell proliferation and angiogenesis.[5]

TGF-β

TGF-β signalling in the tumour microenvironment is a determinant of tumour T-cell exclusion and poor response to PD-1/PD-L1 blockade.[6]

CCL21

CCL21 is a chemokine which promotes immune cell localization in the tumour microenvironment.[7]

CCL21, C-C chemokine motif ligand 21; CD, cluster of differentiation; CTLA-4, cytotoxic T lymphocyte antigen 4; IFN-γ, interferon-γ IL-1β, interleukin-1 beta; LAG, lymphocyte activation gene; MHC, major histocompatibility complex; PD-1, programmed death-1; PD-L1, programmed death-ligand-1; TGF-β, transforming growth factor beta; Treg, regulatory T cell.

1. Pio R, et al. *Front. Immunol*. 2019;10:774; 2. Zou W, et al. *Sci Transl Med*. 2016;8:328rv4; 3. Seidel JA, et al. *Front Oncol*. 2018;8:1–14; 4. He Y, et al. *Cancer Sci*. 2016;107:1193–7; 5. Garon EB, et al. *JTO Clin Res Reports*. 2020;1:100001; 6. Ganesh K, et al. *Immunity*. 2018;48:626–8; 7. Tang H, et al. *Cancer Lett*. 2016;370:85–90.

“Good” and “bad” inflammation

Acute “good” inflammation[1,2]

Cytokines such as **IL-2** and **IL-15** promote:

- Proliferation of T cells
- Generation of cytotoxic T lymphocytes (CTL)
- Maintenance of natural killer (NK) cells

Prolonged immune responses fuel “bad” inflammation[3]

Chronic “bad” inflammation[3,4]

Inflammatory cytokines, including **IL-1β**, **IL-6**, **IL-10** and **TGF-β**, induce:

- Differentiation of regulatory T cells (Treg)
- Differentiation of myeloid-derived suppressor cells (MDSC)
- Inhibition of T-cell proliferation and activity

+ → **Tumour-specific adaptive immunity[3]** ← **-**

By inhibiting tumour-specific immune responses, “bad” inflammation promotes tumour growth and disease progression[3]

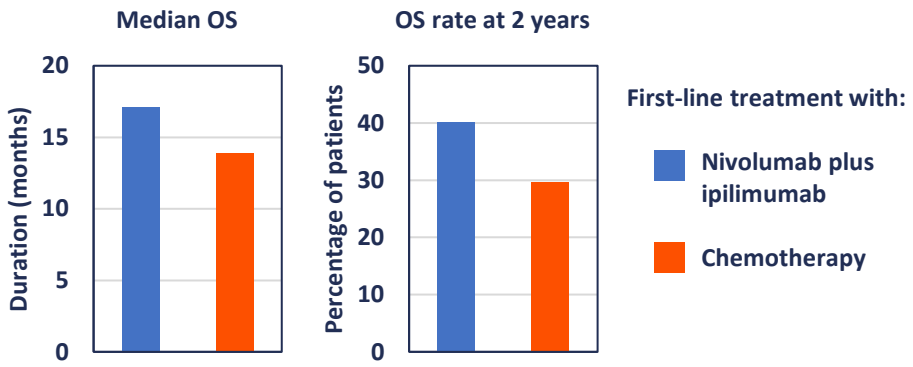
IL-1β, interleukin-1 beta; IL-2, interleukin-2; IL-6, interleukin-6; IL-10, interleukin-10; IL-15, interleukin-15; TGF-β, transforming growth factor beta.

1. Waldmann TA. *Cancer Immunol Res*. 2015;3:219–27; 2. Zhang C, Liu Y. *Front Immunol*. 2020;11:1–20; 3. Wang D, DuBois RN. *Carcinogenesis. 2015;*36:1085–93;
4. Mantovani A, et al. *Immunol Rev*. 2018;281:57–61.

Emerging immunotherapeutic targets in NSCLC

Cell-associated targets

PD-1 + CTLA-4[1]



- Combinations of nivolumab plus ipilimumab are currently being investigated in clinical trials in patients with NSCLC at different stages and with different histories of prior therapies[2,3]

LAG-3[4]

- A phase II trial assessing the effect of LAG-3 blockade in combination with pembrolizumab in NSCLC is currently recruiting (TACTI-002 study, NCT03625323)

CTLA-4, cytotoxic T lymphocyte antigen 4; LAG-3, lymphocyte activation gene 3; NSCLC, non-small cell lung carcinoma; OS, overall survival; PD-1, programmed death-1.

1. Hellmann MD, et al. *N Engl J Med*. 2019;381:2020–3; 2. Remon J, et al. *Cancer Manag Res*. 2019;11:4893–904; 3. Kooshkaki O, et al. *Int J Mol Sci*. 2020;21:4427;
4. NCT03625323. Clinical trials listed by their identifiers at: ClinicalTrials.gov (accessed 17 August 2020).

Emerging immunotherapeutic targets in NSCLC

Soluble targets

TGF-β

- The phase I/II trial NCT02581787 is assessing the effect of inhibition in combination with radiotherapy in early NSCLC[1]

IL-1β

- In a phase III trial on cardiovascular risk (CANTOS, NCT01327846), inhibition of the IL-1β pathway reduced the incidence of lung cancer and lung cancer mortality[2,3]
- Multiple phase III trials are assessing IL-1β blockade in patients with NSCLC[4]

IL-1β, interleukin-1 beta; NSCLC, non-small cell lung carcinoma; TGF-β, transforming growth factor beta.

1. NCT02581787; 2. NCT01327846; 3. Ridker PM, et al. *Lancet*. 2017;390:1833-42; 4. Litmanovich A, et al. *Oncol Ther*. 2018;6:109–27.

Clinical trials listed by their identifiers at: ClinicalTrials.gov (accessed 17 August 2020).

Is IL-1 the key to progress in solid tumours?

Prof. Fabrice Barlesi

Professor of Medicine,
Head of Medical and Clinical Research,
Gustave Roussy,
Villejuif, France

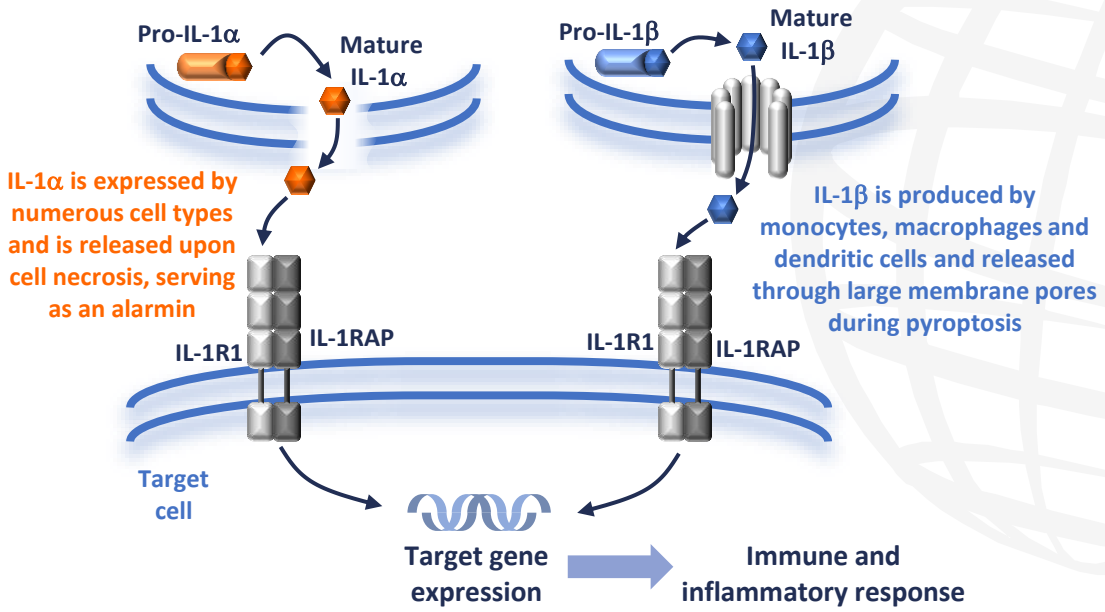
IL-1, interleukin 1.

IL-1 family proteins and their function

The IL-1 family[1]

IL-1 family member	Effect on inflammation
IL-1α	+
IL-1β	+
IL-1Ra	−
IL-18	+
IL-33	+
IL-36α	+
IL-36β	+
IL-36γ	+
IL-36Ra	−
IL-37	−
IL-38	−

IL-1α and IL-1β production[2]



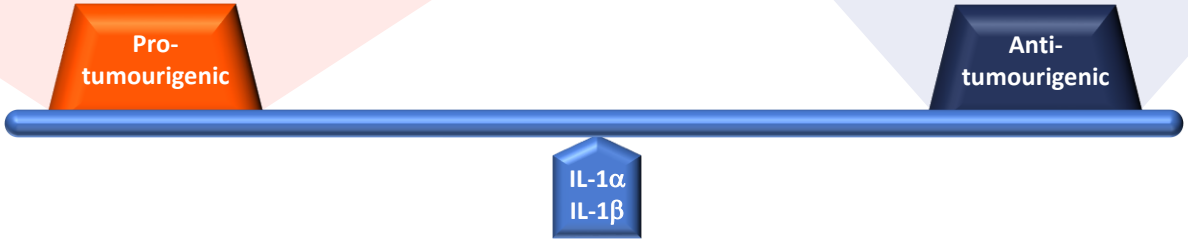
IL-1, interleukin-1; IL-1α, interleukin-1 alpha; IL-1β, interleukin-1 beta; IL-1R1, interleukin-1 receptor 1; IL-1Ra, interleukin-1 receptor antagonist; IL-1RAP, interleukin-1 receptor accessory protein; IL-1R3, interleukin-1 receptor 3; IL-18, interleukin-18; IL-33, interleukin-33; IL-36α, interleukin-36 alpha; IL-36β, interleukin-36 beta; IL-36γ, interleukin-36 gamma; IL-37, interleukin-37; IL-38, interleukin-38.

1. Dinarello CA. *Immunol Rev*. 2018;281:8–27; 2. Garon EB, et al. *JTO Clin Res Reports*. 2020;1:100001.

IL-1 dysregulation in cancer[1–3]

Effect on tumour:	Evidence in:
Angiogenesis	Fibrosarcoma, lung cancer, pancreatic cancer, melanoma, breast cancer
Dedifferentiation	Breast cancer
Invasion and metastasis	Head and neck squamous cell carcinoma, gastric cancer, pancreatic cancer, breast cancer, lung cancer, colorectal cancer
Proliferation	Pancreatic cancer, breast cancer, fibrosarcoma
Tumour-promoting inflammation	Pancreatic cancer, fibrosarcoma
TME modulation	Breast cancer

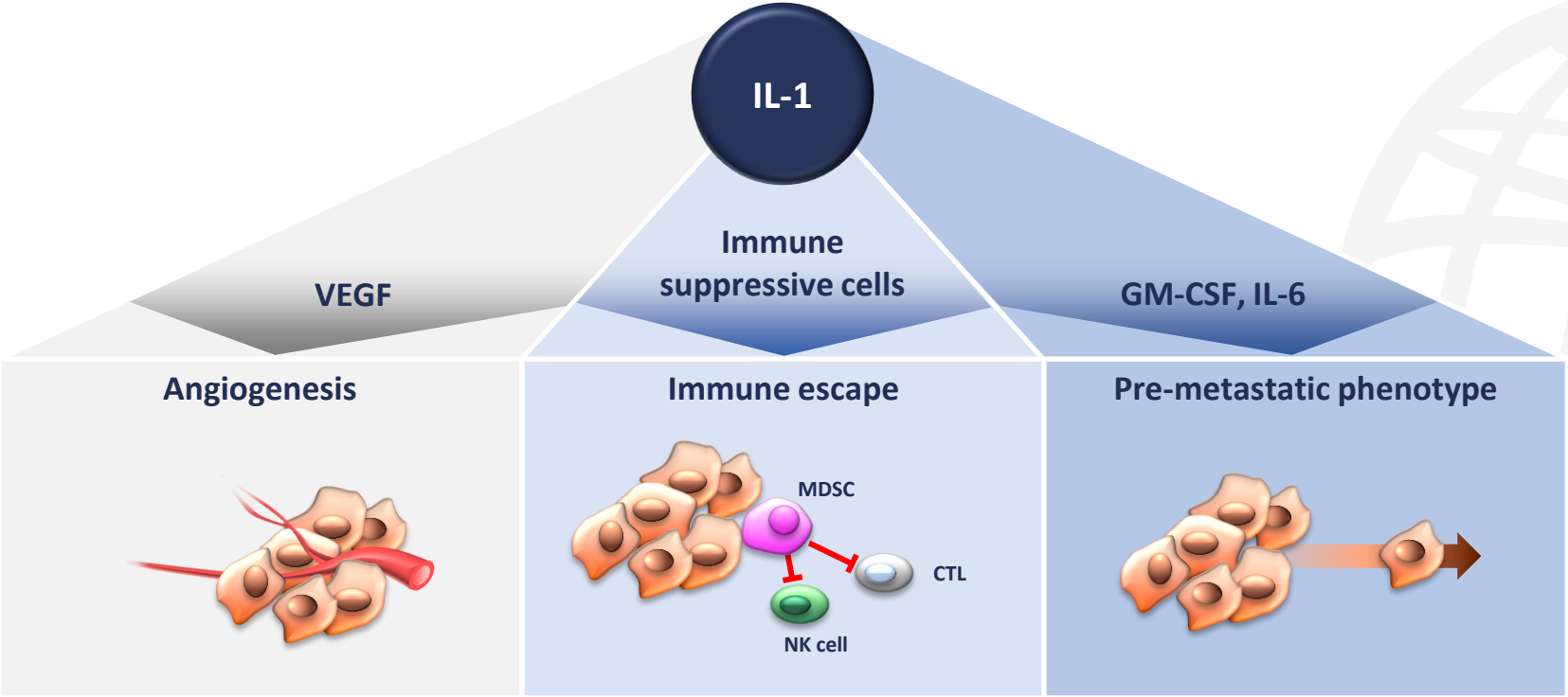
Effect on tumour:	Evidence in:
Immune cell recruitment	Fibrosarcoma, lymphoma, B-cell myeloma
Proliferation	Breast cancer, melanoma, prostate cancer
Metastasis	Breast cancer



IL-1, interleukin-1; IL-1α, interleukin-1 alpha; IL-1β, interleukin-1 beta; TME, tumour microenvironment.

1. Van Gorp H, Lamkanfi M. *EMBO Rep*. 2019;20:1–15; 2. Garon EB, et al. *JTO Clin Res Reports*. 2020;1:100001; 3. Baker KJ, et al. *Front Immunol*. 2019;10:1197.

IL-1 dysregulation in cancer[1]



CTL, cytotoxic T lymphocyte; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-1, interleukin-1; IL-6, interleukin-6; MDSC, myeloid-derived suppressor cell; NK, natural killer; VEGF, vascular endothelial growth factor.

1. Van Gorp H, Lamkanfi M. *EMBO Rep*. 2019;20:1–15.

Investigational drugs targeting IL-1 for the treatment of solid tumours

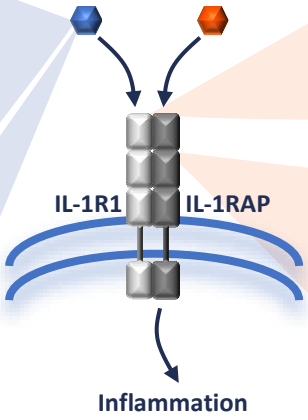
Drugs inhibiting IL-1β signalling

Canakinumab
mAb against IL-1β

- NCT03447769, phase III, NSCLC[1]
- NCT03631199, phase III, NSCLC[2]
- NCT03626545, phase III, NSCLC[3]
- NCT03968419, phase II, NSCLC[4]
- NCT02900664, phase I, CRC, breast cancer, NSCLC[5]
- NCT03742349, phase I, breast cancer[6]
- NCT04028245, phase I, renal cell carcinoma[7]

Gevokizumab
mAb against IL-1β

- NCT03798626, phase I, metastatic colorectal, gastroesophageal and renal cancers[8]



Drugs inhibiting IL-1α and IL-1β signalling

Anakinra
Recombinant IL-1R antagonist

- NCT01624766, phase I, advanced cancers[9]
- NCT02550327, phase I, pancreatic cancer[10]

CAN04
mAb targeting IL-1RAP

- NCT03267316, phase I/II, NSCLC, pancreatic ductal adenocarcinoma, triple-negative breast cancer, CRC[11]
- NCT04452214, phase I, NSCLC, urothelial carcinoma, malignant melanoma, HNSCC[12]

CRC, colorectal cancer; HNSCC, head and neck non-squamous cell carcinoma; IL-1, interleukin-1; IL-1α, interleukin-1 alpha; IL-1β, interleukin-1 beta; IL-1R, interleukin-1 receptor; IL-1RAP, interleukin-1 receptor accessory protein; mAb, monoclonal antibody; NSCLC, non-small cell lung carcinoma.

1. NCT03447769; 2. NCT03631199; 3. NCT03626545; 4. NCT03968419; 5. NCT02900664; 6. NCT03742349; 7. NCT04028245; 8. NCT03798626; 9. NCT01624766; 10. NCT02550327; 11. NCT03267316; 12. NCT04452214. Clinical trials listed by their identifiers at: ClinicalTrials.gov (accessed 25 August 2020).

IL-1β as a future option for NSCLC immunotherapy

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IL-1β, interleukin-1 beta; NSCLC, non-small cell lung carcinoma.

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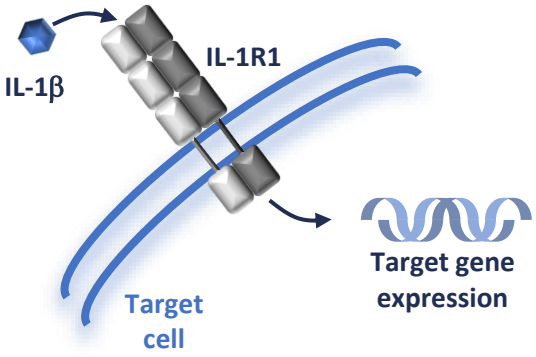
IL-1β as a target for immunotherapy[1]



- GM-CSF
- Chemokine
- Leukocyte adhesion molecules
- COX2–PGE2 pathway
- miRNA regulation

- Recruitment of MDSC
- Promotion of tumour invasiveness
- Immune suppression and immune evasion
- Apoptosis resistance
- Promotion of angiogenesis

Drugs targeting IL-1 signalling approved for the treatment of autoinflammatory syndromes	
Rilonacept	Recombinant IL-1R fusion protein
Anakinra	Recombinant IL-1R antagonist
Canakinumab	Monoclonal antibody against IL-1β

COX2, cyclooxygenase 2; IL-1β, interleukin-1 beta; IL-1R, interleukin-1 receptor; GM-CSF, granulocyte-macrophage colony-stimulating factor MDSC, myeloid-derived suppressor cells; miRNA, micro ribonucleic acid; PGE2, prostaglandin E2.

1. Garon EB, et al. *JTO Clin Res Reports*. 2020;1:100001.

CANTOS: Study design[1]

N=10,061

- History of myocardial infarction
- Blood hsCRP level ≥ 2 mg/L
- No history of chronic infection, malignancies or immunodeficiency

Placebo
plus standard care
(n=3,344)

Canakinumab 50 mg
plus standard care
(n=2,170)

Canakinumab 150 mg
plus standard care
(n=2,284)

Canakinumab 300 mg
plus standard care
(n=2,263)

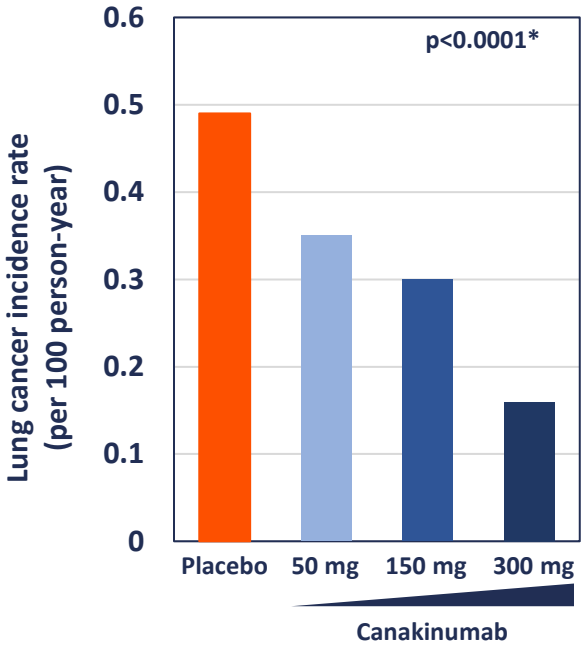
Effect of IL-1β inhibition on atherosclerosis and risk for cardiovascular disease

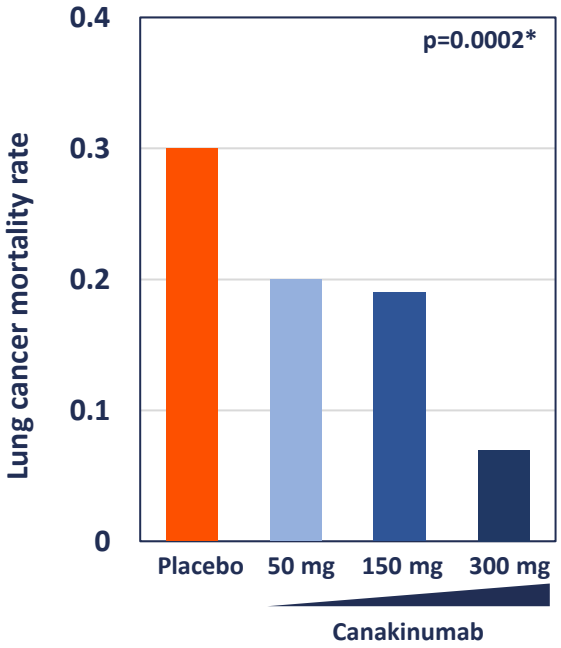
Participants were followed up for incident cancer diagnoses

hsCRP, high-sensitivity C-reactive protein; IL-1β, interleukin-1 beta.

1. Ridker PM, et al. *Lancet*. 2017;390:1833–42.

CANTOS: Clinical outcomes[1]

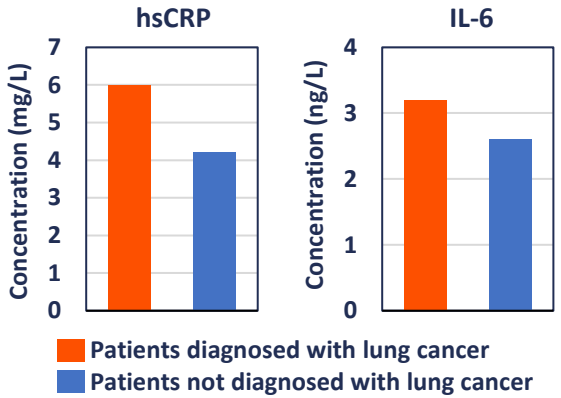


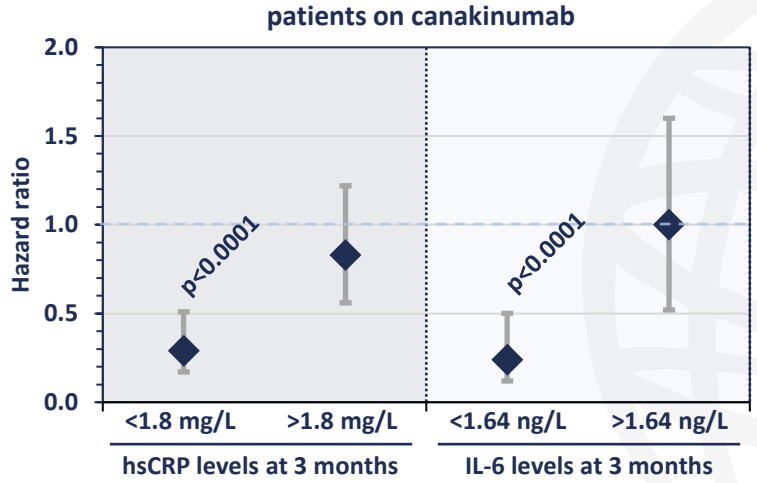


! Canakinumab could reduce incident lung cancer and lung cancer mortality

1. Ridker PM, et al. *Lancet*. 2017;390:1833–42.

CANTOS: Biomarkers analyses[1]





hsCRP
26–41% reduction

IL-6
25–43% reduction

With canakinumab compared with placebo
(3.7 years' follow-up)

! The benefit of canakinumab on lung cancer was observed only in patients with low plasma levels of hsCRP and IL-6

hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6.

1. Ridker PM, et al. *Lancet*. 2017;390:1833–42.

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Clinical trials testing IL-1β inhibition in NSCLC

CANOPY-A[1] Phase III NCT03447769	CANOPY-1[2] Phase III NCT03631199	CANOPY-2[3] Phase III NCT03626545
• N=1,500 (estimated; recruiting) • Stages II–IIIA and IIIB, completely resected NSCLC	• N=673 (actual; not recruiting) • Advanced or metastatic NSCLC • No prior treatment	• N=245 (actual; not recruiting) • NSCLC • Prior treatment with PD-1 or PD-L1 inhibitors and Pt-chemo
Canakinumab as adjuvant therapy vs Placebo	**Canakinumab** + pembro + Pt-chemo vs Placebo + pembro + Pt-chemo	**Canakinumab** + docetaxel vs Placebo + docetaxel

Early stage clinical trials

CANOPY-N[4] Phase II NCT03968419	CANFOUR[5] Phase I/II NCT03267316	CAN04CLIN002[6] Phase I NCT04452214
• Early stage NSCLC • Canakinumab alone or in combination with pembro	• Solid tumours, including NSCLC • CAN04 (mAb against IL-1RAP) alone or in combination with chemotherapy	• Solid tumours, including NSCLC • CAN04 (mAb against IL-1RAP) in combination with pembro

IL-1β, interleukin-1 beta; IL-1RAP, interleukin-1 receptor accessory protein; mAb, monoclonal antibody; NSCLC, non-small cell lung carcinoma; pembro, pembrolizumab; PD-1, programmed death-1; PD-L1, programmed death-ligand-1; Pt-chemo, platinum-based chemotherapy.

1. NCT03447769; 2. NCT03631199; 3. NCT03626545; 4. NCT03968419; 5. NCT03267316; 6. NCT04452214. Clinical trials listed by their identifiers at: ClinicalTrials.gov (accessed 03 September 2020).

COVID-19 and lung cancer management

Dr Marina Garassino

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Milan, Italy

COVID-19, coronavirus disease 2019.

Impact of COVID-19 on lung cancer patients

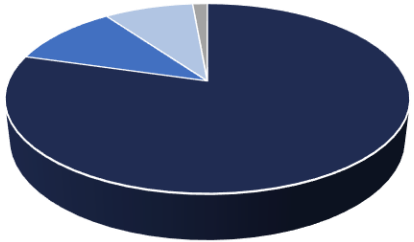
TERAVOLT study[1,2]:
- Recruitment ongoing
- Data reported on N=400 patients with any thoracic cancer and a COVID-19 diagnosis

334 patients hospitalized

33 patients admitted to ICU

20 patients on mechanical ventilation

141 deaths (35.5%)



COVID-19, coronavirus disease 2019; ICU, intensive care unit; TERAVOLT, Thoracic Cancers International COVID-19 Collaboration.

1. Garassino MC, et al. *Lancet Oncol.* 2020;21:914–22; 2. Horn L, et al. Presented at the ASCO20 Virtual Meeting, 2020 [Abstract LBA111].

Risk factors for COVID-19-related death

	Patients with thoracic cancer (TERAVOLT)[1]	General population (UK data)[2]
Older age (≥65 years old)	✓	✓
Gender (male)	✗	✓
Comorbidities	✓	✓
Ethnicity (black/south Asian)	✗	✓
Smoking	✗	Not assessed
ECOG performance status	✓	Not applicable
Stage of cancer	✗	Not applicable

COVID-19, coronavirus disease 2019; ECOG, Eastern Cooperative Oncology Group; TERAVOLT, Thoracic Cancers International COVID-19 Collaboration.

1. Horn L, et al. . Presented at the ASCO20 Virtual Meeting, 2020 [Abstract LBA111]; 2. Williamson EJ, et al. *Nature*. 2020. doi: 10.1038/s41586-020-2521-4 [Online ahead of print].

COVID-19 and care of patients with lung cancer

EU UK Japan

Guidelines to minimize contact while preserving a high standard of care[1–3]

Hospital visits

- Avoid if unnecessary
- Use telemedicine and phone consultation when possible

Treatment

- Use schedules which reduce hospital time
- Delay treatment if the benefit for the patient is uncertain

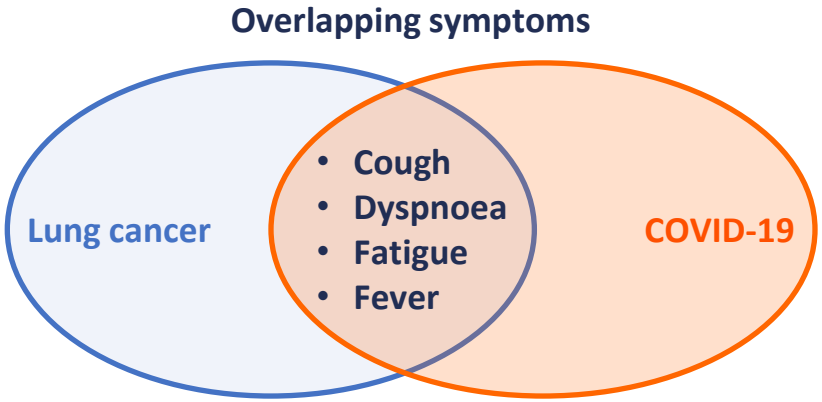
Screening

- Deferred during the pandemic
- When restarting, screenings should be considered on a patient-by-patient basis

COVID-19, coronavirus disease 2019.

1. European Society for Medical Oncology. ESMO management and treatment adapted recommendations in the COVID-19 era: lung cancer. Available at: www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic/lung-cancer-in-the-covid-19-era (accessed on 26 August 2020); 2. British Thoracic Society. Lung cancer and mesothelioma service guidance during the COVID-19 pandemic, available at: www.brit-thoracic.org.uk/document-library/quality-improvement/covid-19/lung-cancer-pathway-guidance-covid-19/ (accessed 26 August 2020);
3. Mori M, et al. *Surg Today*. 2020;50:794–808.

COVID-19 and imaging for lung cancer[1–4]



- The radiological manifestations of COVID-19 pneumonia can overlap with CT findings in patients with lung cancer[1]
- A swab or serological test may be required for differential diagnosis of lung cancer and COVID-19

ESMO, European society for medical oncology; COVID-19, coronavirus disease 2019; CT, computed tomography.

1. Calabrò L, et al. *Lancet Respir Med.* 2020;8:542–4; 2. European Society for Medical Oncology. ESMO management and treatment adapted recommendations in the COVID-19 era: lung cancer. Available at: www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic/lung-cancer-in-the-covid-19-era (accessed 26 August 2020); 3. British Thoracic Society. Differentiation of the Cs in lung cancer: Cancer vs. COVID. Available at www.btog.org/latest/covid-19-information-for-thoracic-oncology-healthcare-professionals/ (accessed 26 August 2020); 4. Pasikhova Y, et al. *Cancer Control.* 2017;24:193–7.

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Lung cancer management after COVID-19

Telemedicine may be used after the pandemic to limit unnecessary hospital visits

- Need to consider accessibility to the internet and necessary technology, particularly for elderly patients
- The median age of lung cancer patients at diagnosis is around 70 years old

New guidelines will need to consider the potential impact of chemotherapy on COVID-19

- Prior administration of chemotherapy is associated with increased risk of death, while immunotherapy or TKI are not[1]

COVID-19, coronavirus disease 2019; TKI, tyrosine kinase inhibitor.

1. Horn L, et al. Presented at the ASCO20 Virtual Meeting, 2020. [Abstract LBA111].