Targeting IL-1β in NSCLC: What does the future hold?

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Agenda

Immunotherapy for NSCLC today: Where are we?

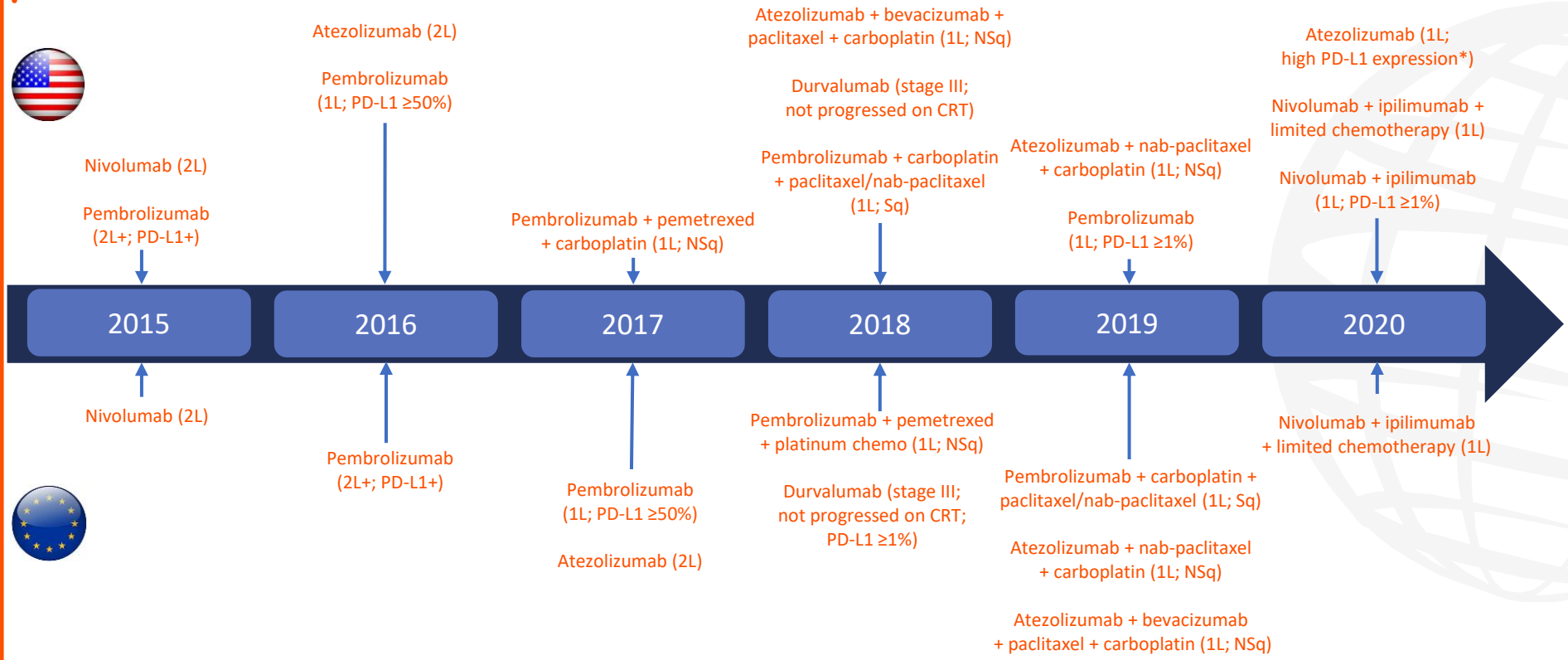
What is the rationale for targeting IL-1β in NSCLC and which agents are currently in clinical development?

How could IL-1β inhibition be implemented in the management of NSCLC?

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

Immunotherapy for NSCLC today: Where are we?

Immune checkpoint blockade therapy for NSCLC



*PD-L1 stained ≥50% of tumour cells or PD-L1 stained tumour-infiltrating immune cells covering ≥10% of the tumour area.
1L, first line; 2L, second line; CRT, chemoradiotherapy; NSCLC, non-small cell lung cancer; NSq, non-squamous; PD-L1, programmed death-ligand 1; Sq, squamous.
Approval information available at: U.S. Food & Drug Administration www.fda.gov and European Medicines Agency www.ema.europa.eu.

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5-year survival with ICI monotherapy in advanced NSCLC

Trial	Checkpoint inhibitor	Prior treatment	PD-L1 expression	Number of patients	5-year OS (%)
CA209-003[1]	Nivolumab	Previously treated	Any	129	16
CheckMate 057 + 017[2–4]	Nivolumab	Previously treated	Any	427	13.4
KEYNOTE-001[5]	Pembrolizumab	Previously treated Treatment naïve	Any TPS ≥1%	449 101	15.5 23.2
KEYNOTE-024[6]	Pembrolizumab	Treatment naïve	TPS ≥50%	154	31.9

ICIs provide long-term OS benefit and durable responses with a tolerable safety profile, but only in a subset of patients

ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed death-ligand 1; TPS, tumour proportion score.

1. Gettinger S, et al. *J Clin Oncol.* 2018;36:1675–84; 2. Borghaei H, et al. *J Clin Oncol.* 2021;JCO2001605. doi:10.1200/JCO.20.01605 (Online ahead of print);
3. Brahmer J, et al. *N Engl J Med.* 2015;373:123–35; 4. Borghaei H, et al. *N Engl J Med.* 2015.373:1627–39; 5. Garon E, et al. *J Clin* Oncol. 2019;37:2518–27;
6. Brahmer JR, et al. *Ann Oncol.* 2020;31(Suppl. 4):S1142–215.

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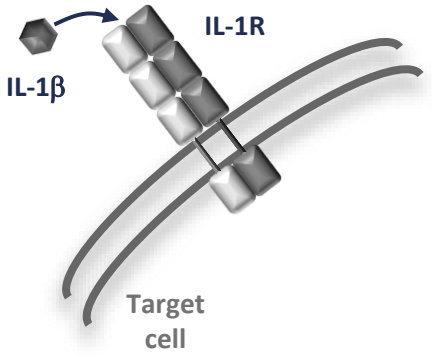
What is the rationale for targeting IL-1β in NSCLC and which agents are currently in clinical development?

IL-1β as a target for immunotherapy

IL-1β is a pro-inflammatory cytokine which binds to IL-1R1 on the surface of target cells[1]



Mechanisms by which IL-1β drives tumourigenesis include:

- Modulation of epithelial-mesenchymal transition[1]
- Tumour growth, invasiveness, metastasis and angiogenesis[1]
- Apoptosis resistance[1]
- Promotion of an immunosuppressive tumour microenvironment[2]

IL-1β, interleukin-1 beta; IL-1R, interleukin-1 receptor; IL-1R1, interleukin-1 receptor type 1.

1. Garon EB, et al. *JTO Clin Res Reports*. 2020;1(1):100001; 2. Gelfo V, et al. *Int J Mol Sci.* 2020;21:6009.

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IL-1-targeting agents under investigation for cancer

Agent	Mechanism of action	Trial phase	Tumour site
Anakinra[1]	Recombinant IL-1Ra	I	Relapsed or refractory advanced cancers
Canakinumab[2–5]	mAb directed against IL-1β	II,III	NSCLC
CAN04[6,7] (nidanilimab)	mAb against the IL-1R accessory protein	I,II	Solid tumours, including NSCLC
Gevokizumab[8,9]	Allosteric mAb directed against IL-1β	I	Metastatic colorectal, gastro-oesophageal and renal cancers
Isunakinra[10]	IL-1β/IL-1Ra fusion protein	I	Metastatic or unresectable advanced solid tumours

IL-1β, interleukin-1 beta; IL-1Ra, interleukin-1 receptor antagonist; IL-1R, interleukin-1 receptor; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer.

1. NCT01624766; 2. NCT03447769; 3. NCT03968419; 4. NCT03631199; 5. NCT03626545; 6. NCT04452214; 7. NCT03267316; 8. NCT03798626;
9. Issafras H, et al. *J Pharmacol Exp Ther.* 2014;348:202–159; 10. NCT04121442.

Clinical trial information available from clinicaltrials.gov (accessed 2 February 2021).

How can IL-1β inhibition be implemented in the management of NSCLC?

Clinical trials exploring drugs targeting IL-1β for the treatment of NSCLC

Monotherapy

- Canakinumab vs placebo[1] (NCT03447769; CANOPY-A; adjuvant)
- Canakinumab vs pembrolizumab vs both[2] (NCT03968419; CANOPY-N; neoadjuvant)
- Isunakinra[3] (NCT04121442; dose study; ≥1 prior line of therapy)

+ chemo

- Canakinumab + docetaxel vs docetaxel alone[4] (NCT03626545; CANOPY-2; prior platinum chemotherapy and PD-(L)1 inhibitor)
- CAN04 + cisplatin, gemcitabine, or nab-paclitaxel[5] (NCT03267316; CANFOUR; first or second line)

+ chemo + checkpoint inhibitor

- Canakinumab + chemo+ pembrolizumab vs chemo + pembrolizumab[6] (NCT03631199; CANOPY-1; first line)

+ checkpoint inhibitor

- CAN04 + pembrolizumab[7] (NCT04452214; progression on PD-(L)1 inhibitor-containing regimens)

+ mTOR kinase inhibitor

- Everolimus plus anakinra vs everolimus or denosumab[8] (NCT01624766; relapsed/refractory disease)

Chemo, chemotherapy; IL-1β, interleukin-1 beta; NSCLC, non-small lung cancer; mTOR, mechanistic target of rapamycin.

1. NCT03447769; 2. NCT03968419; 3. NCT04121442; 4. NCT03626545; 5. NCT03267316; 6. NCT03631199; 7. NCT04452214; 8. NCT01624766.

Clinical trial information available from clinicaltrials.gov (accessed 2 February 2021).