

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

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Expert panel



Dr Pilar Garrido

Associate Professor of
Medical Oncology,
University of Alcalá,
Head of Thoracic
Tumours Section,
University Hospital Ramón y Cajal,
Madrid, Spain



Dr Barbara Melosky

Professor of Medicine,
University of British Columbia,
Medical Oncologist,
BC Cancer,
Vancouver, Canada



Dr Alastair Greystoke

Clinical Senior Lecturer and
Honorary Consultant,
Sir Bobby Robson Clinical
Trials Unit,
Freeman Hospital,
Newcastle upon Tyne, UK



Agenda

Immunotherapy for NSCLC today: Where are we?

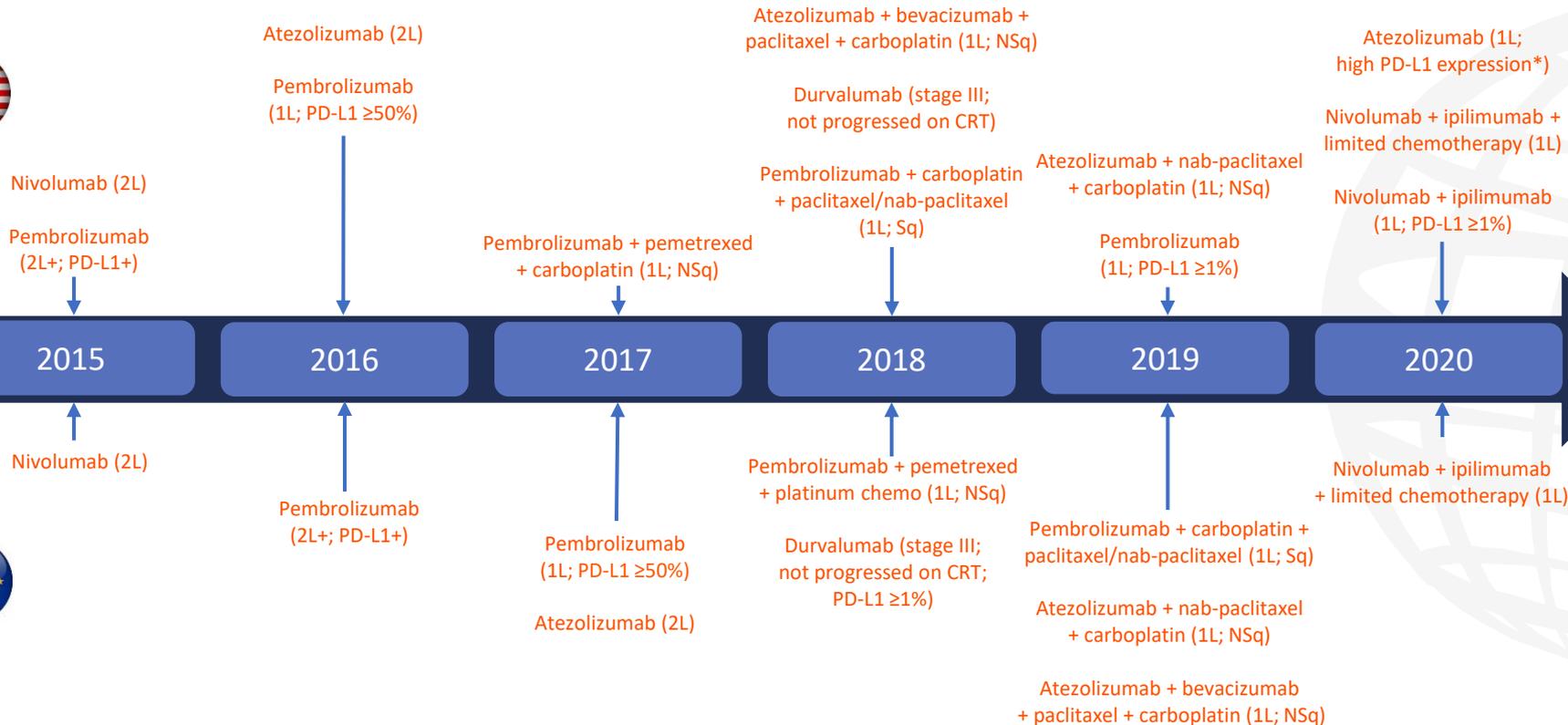
What is the rationale for targeting IL-1 β in NSCLC and which agents are currently in clinical development?

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



**Immunotherapy for NSCLC today:
Where are we?**

Immune checkpoint blockade therapy for NSCLC



*PD-L1 stained $\geq 50\%$ of tumour cells or PD-L1 stained tumour-infiltrating immune cells covering $\geq 10\%$ 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.

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	Any	449	15.5
		Treatment naïve	TPS ≥1%	101	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

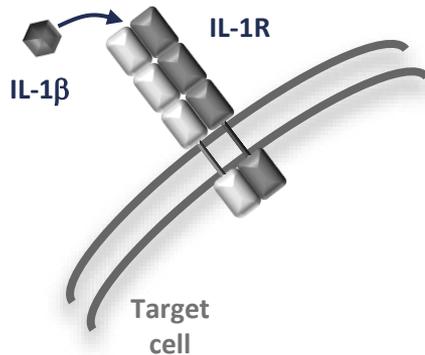
ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed death-ligand 1; TPS, tumour proportion score.
 1. Gettinger S, et al. *J Clin Oncol*. 2018;36:1675–84; 2. Borghaei H, et al. *J Clin Oncol*. 2021;JCO2001605. doi:10.1200/JCO.20.01605 (Online ahead 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.



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

IL-1 β as a target for immunotherapy

IL-1 β is a pro-inflammatory cytokine which binds to IL-1R1 on the surface of target cells¹



Mechanisms by which IL-1 β drives tumourigenesis include:

- Modulation of epithelial-mesenchymal transition¹
- Tumour growth, invasiveness, metastasis and angiogenesis¹
- Apoptosis resistance¹
- Promotion of an immunosuppressive tumour microenvironment²

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-1 β	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-1 β	I	Metastatic colorectal, gastro-oesophageal and renal cancers
Isunakinra ¹⁰	IL-1 β /IL-1Ra fusion protein	I	Metastatic or unresectable advanced solid tumours

IL-1 β , 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-1 β inhibition be implemented
in the management of NSCLC?**

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

Monotherapy

- Canakinumab vs placebo¹
(NCT03447769; CANOPY-A; adjuvant)
- Canakinumab vs pembrolizumab vs both² (NCT03968419; CANOPY-N; neoadjuvant)
- Isunakinra³
(NCT04121442; dose study; ≥ 1 prior line of therapy)

+ chemo

- Canakinumab + docetaxel vs docetaxel alone⁴
(NCT03626545; CANOPY-2; prior platinum chemotherapy and PD-(L)1 inhibitor)
- CAN04 + cisplatin, gemcitabine, or nab-paclitaxel⁵
(NCT03267316; CANFOUR; first or second line)

+ chemo + checkpoint inhibitor

- Canakinumab + chemo+ pembrolizumab vs chemo + pembrolizumab⁶
(NCT03631199; CANOPY-1; first line)

+ checkpoint inhibitor

- CAN04 + pembrolizumab⁷
(NCT04452214; progression on PD-(L)1 inhibitor-containing regimens)

+ mTOR kinase inhibitor

- Everolimus plus anakinra vs everolimus or denosumab⁸
(NCT01624766; relapsed/refractory disease)

Chemo, chemotherapy; IL-1 β , 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.

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