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Uncharted territory: Introducing novel immunotherapeutic approaches for metastatic NSCLC without driver mutations

Practice aid for metastatic NSCLC education

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Guidelines for first-line immunotherapy for mNSCLC without driver mutations

NCCN[1]

Patients with PD-L1 expression ≥50% (PS=0–2)

- **Pembrolizumab, atezolizumab or cemiplimab (cat 1, preferred)**
- **Pembrolizumab + CT (cat 1, preferred)**

Some other recommendations:*

- Atezolizumab ± bevacizumab + CT (cat 1 for + bevacizumab)†
- Nivolumab + ipilimumab ± CT (cat 1)‡
- Cemiplimab + CT (cat 1)
- Tremelimumab + durvalumab + CT (cat 1; cat 2B)§

Patients with PD-L1 expression 1–49%, (PS=0–2)

- **Pembrolizumab + CT (cat 1, preferred)**
- Pembrolizumab (cat 2B)

Some other recommendations (see above)

Patients with PD-L1 expression <1%

- PS 0–1: As per recommendations for PD-L1 expression 1–49%¶; PS 2: CT; PS 3–4: Best supportive care

ESMO[2]

Patients with PD-L1 expression ≥50% (PS=0–1)

- **Pembrolizumab (I, A; preferred)**
- Atezolizumab or cemiplimab monotherapy (I, A)
- Nivolumab + ipilimumab + 2 cycles of CT (optional pemetrexed maintenance for non-squamous histology) (IV, B)#

Patients with PD-L1 expression <50% (PS=0–1)

- Pembrolizumab + CT (I, A)
- Atezolizumab ± bevacizumab + CT (I, A)†
- Nivolumab + ipilimumab + 2 cycles of CT (optional pemetrexed maintenance) (I, A)
- Tremelimumab + durvalumab + CT (I, A)

Not EMA approved:

- Cemiplimab + CT (I, A)
- Nivolumab + ipilimumab for PD-L1 expression ≥1% (I, A)

*List not exhaustive; †Recommended for non-squamous histology only; ‡Nivolumab + ipilimumab useful in certain circumstances (cat 1); §Cat 1 recommendation for PD-L1 expression 1–49% non-squamous histology, cat 2B for PD-L1 expression ≥50% and 1–49% squamous histology; ¶Pembrolizumab monotherapy not recommended, nivolumab + ipilimumab is recommended (no category provided), and tremelimumab + durvalumab + CT not category 1 recommended for PD-L1 expression <1%; #Option for patients without contraindication for immunotherapy and needing a fast tumour load reduction.

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Novel immunotherapeutic mechanisms of action for patients with non-driver mutation mNSCLC

- New immune checkpoints have been identified and are under investigation in clinical trials in NSCLC and include **LAG-3**, **TIM-3** and **TIGIT**[3]
- A combination approach using novel targets and existing PD-1/PD-L1 and CTLA-4 inhibitors may provide a synergistic effect and enhanced clinical efficacy[3]

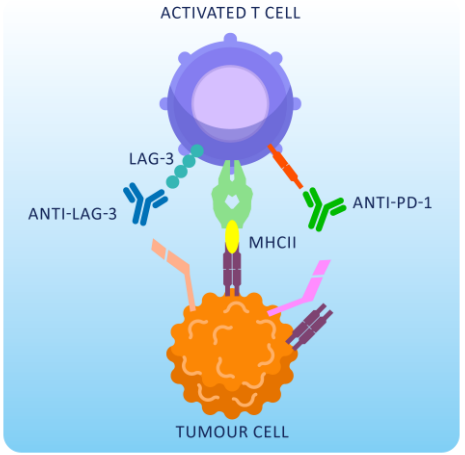
LAG-3

TM protein usually expressed on CD4+ and CD8+ T cells, Tregs, NK cells, B cells and plasmacytoid DCs[3]

Interacts with MHCII to prohibit its binding to TCR and CD4, thus directly hindering TCR signalling.[4] LAG-3 signalling negatively regulates T cell activation, proliferation and cytokine secretion[3,4]

During tumourigenesis/cancer progression, tumour cells exploit this pathway to escape immune surveillance[3]

Anti-LAG-3 mechanism of action[5,6]



Key emerging LAG-3 inhibitors and ongoing clinical trials in stage IV/recurrent or mNSCLC

Eftilagimod alpha

- TACTI-002 (phase II): **Eftilagimod alpha** + pembrolizumab (anti-PD-1) in mNSCLC[7]
  - Data cut-off Jan 2022: ORR 37%

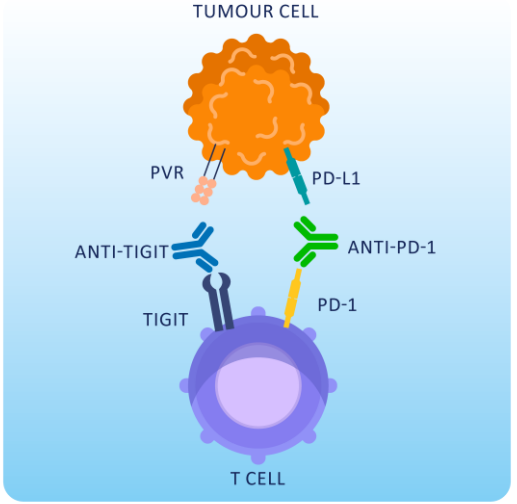
Relatlimab

- RELATIVITY-104 (phase II): **Relatlimab** + nivolumab (anti-PD-1) + CT in stage IV or recurrent NSCLC[8]

TIGIT

- TM protein expressed on T cell subsets (including Tregs and memory T cells) and NK cells[3,9]
- Binds multiple ligands, including PVR, nectin-2, -3, and -4. Activated TIGIT transmits inhibitory signals through ITIM and ITT-like motifs in its cytoplasmic domain, reducing T cell stimulation and NK cell cytotoxicity[9–11]
- In cancer, TIGIT is co-expressed with PD-1 on tumour antigen-specific T cells and TILs. Dual PD-1 and TIGIT blockade with immunotherapy is a promising therapeutic strategy[12]

Anti-TIGIT mechanism of action[9,12]



Key emerging TIGIT inhibitors and ongoing clinical trials in advanced or mNSCLC

Tiragolumab

- CITYSCAPE (phase II): **Tiragolumab** + atezolizumab vs PBO + atezolizumab in PD-L1-positive recurrent or mNSCLC[13]
  - June 2019 data cut-off: ORR 31.3% vs 16.2%; mPFS 5.4 vs 3.6 months (tiragolumab vs PBO)
- SKYSCRAPER-01 (phase III): **Tiragolumab** + atezolizumab vs atezolizumab alone in patients with PD-L1 high, locally advanced, unresectable or mNSCLC[14]
  - Interim analysis: PFS not met; OS immature analysis
- SKYSCRAPER-03 (phase III): **Tiragolumab** + atezolizumab vs durvalumab in patients with locally advanced, unresectable stage III NSCLC[15]
- SKYSCRAPER-06 (phase II/III): **Tiragolumab** + atezolizumab + CT vs PBO + pembrolizumab + CT in untreated advanced NSCLC[16]

Domvanalimab

- ARC-7 (phase II): **Domvanalimab** + zimberelimab (anti-PD-1; DZ) ± etrumadenant (anti-A2aR and A2bR; EDZ) vs zimberelimab (Z) in PD-L1-high mNSCLC[17]
  - August 2022 data cut-off : ORR 41%, 40%, 27%; mPFS 12.0, 10.9, 5.4 months (DZ, EDZ, Z)

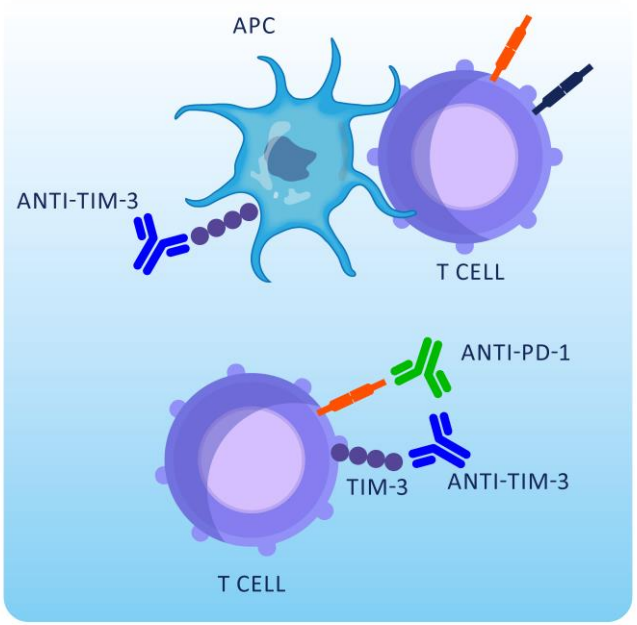
TIM-3

TM protein expressed on T cells, B cells, Tregs, NK cells, DCs, monocytes and macrophages. Binds several ligands, including galectin-9, HMGB1, CEACAM1, and PtdSer[18]

In its unbound state, TIM-3 can interact with Bat-3 and maintain T cell activation via TCR signalling. TIM-3 can also suppress NF-kB-mediated activation of DCs by sequestering HMGB1.[18,19]

In cancer, TIM-3 expression marks the most terminally exhausted subset of CD8+ T cells. Dual PD-1 and TIM-3 blockade with immunotherapy is a promising therapeutic strategy.[19]

Anti-TIM-3 mechanism of action[18,20]



Key emerging TIM-3 inhibitors and ongoing clinical trials in advanced NSCLC

Cobolimab

- **AMBER (phase I):** **Cobolimab** or cobolimab + nivolumab (anti-PD-1) or cobolimab + dostarlimab (anti-PD-1) in advanced solid tumours (including NSCLC)[21]
  - Manageable safety profile of cobolimab monotherapy and combination with dostarlimab
- **COSTAR Lung (phase II/III):** **Cobolimab** + dostarlimab + CT vs dostarlimab + CT vs CT alone in patients with advanced or metastatic NSCLC who have progressed on anti-PD-(L)1 treatment[22]

Bispecific antibodies[23]

Recombinant molecules containing two different antigens or epitopes identifying binding domains

Bispecific immunotherapeutic antibodies can simultaneously target two inhibitory checkpoints expressed on the surface of the same or different cells

Key emerging bispecific antibodies and ongoing clinical trials in advanced or metastatic NSCLC

MEDI5752 (Bispecific antibody targeting PD-1/CTLA-4)[24]

- **NCT03530397 (phase Ib/II)**: MEDI5752 + CT vs pembrolizumab + CT 1L in mNSCLC
  - July 2022 data cut-off: 1500 mg MEDI5752 improved survival vs pembrolizumab, but with high TEAEs and discontinuation
  - 750 mg dose is now being investigated

AZD2936 (Bispecific antibody targeting PD-1/TIGIT)[25]

- **ARTEMIDE-01 (phase I/II dose expansion):** Advanced or mNSCLC

ADCs[26]

ADCs consist of a cytotoxic drug, or 'payload', conjugated to a mAb targeting a specific antigen expressed on cancer cells

The ultimate goal of an ADC is to maximize tumour cell kill, while minimizing systemic toxicity to healthy cells

Key emerging ADCs and ongoing clinical trials in advanced or mNSCLC

Sacituzumab-govitecan (Anti-Trop-2 antibody linked to a cytotoxic SN-38 payload)[27]

- **EVOKE-02 (phase II):** Sacituzumab govitecan + pembrolizumab ± CT 1L in advanced NSCLC

Datopotamab deruxtecan (Anti-Trop-2 antibody linked to a cytotoxic deruxtecan payload)[28]

- **TROPION-Lung08 (phase III):** Datopotamab deruxtecan + pembrolizumab vs pembrolizumab alone in PD-L1 ≥50% advanced or mNSCLC

Abbreviations and References

Abbreviations

1L, first-line; A2aR, adenosine A2a receptor; A2bR, adenosine A2b receptor; ADC, antibody-drug conjugate; APC, antigen-presenting cell; Bat-3, HLA-B-associated transcript 3; cat, category; CEACAM1, carcinoembryonic antigen-related cell adhesion molecule 1; CT, chemotherapy; CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; DC, dendritic cell; DZ, domvanalimab + zimberelimab; EDZ, etrumadenant + domvanalimab + zimberelimab; EMA, European Medicines Agency; ESMO, European Society for Medical Oncology; HMGB1, high mobility group box protein 1; ITIM, immunoreceptor tyrosine-based inhibitory motif; ITT, immunoreceptor tyrosine tail; LAG-3, major histocompatibility complex class II ligand lymphocyte activation gene-3; mAb, monoclonal antibody; MHCII, major histocompatibility complex class II; mNSCLC, metastatic NSCLC; mPFS, median PFS; NCCN, National Comprehensive Cancer Network; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NK, natural killer; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PBO, placebo; PD-(L)1, programmed cell death (ligand)-1; PFS, progression free survival; PS, performance status; PtdSer, phosphatidylserine; PVR, poliovirus receptor; TCR, T cell receptor; TEAE, treatment-emergent adverse event; TIGIT, T-cell immunoglobulin and ITIM domain; TIL, tumour infiltrating lymphocyte; TIM-3, T cell immunoglobulin and mucin domain-containing protein 3; TM, transmembrane; Treg, regulatory T cell; Trop-2, trophoblast cell-surface antigen 2; Z, zimberelimab.

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