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Perspectives on *EGFR*-mutant and wildtype NSCLC: Tailoring treatment advances in late-stage disease

Clinical summary for Module 2: *EGFR*-wildtype NSCLC

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Advances in *EGFR*-wildtype NSCLC to address unmet needs

Research to focus on effective therapies after first-line treatment

"Only about 50% of patients will respond to first-line treatment and nearly all patients will relapse and have disease progression at some point. This is where the real unmet need is: options for patients who progress after immunotherapy are really limited."

Faculty and topics

Dr Helena Yu, CD presented the key clinical trials that are aiming to address unmet needs in patients with metastatic *EGFR*-wildtype NSCLC

Key areas for research

Novel combinations

- Dual checkpoint inhibition to help enhance the immune response[1]
- Combining targeted therapy with immunotherapy[1]

Novel treatments

- Novel immunotherapies, e.g. anti-LAG3 and anti-TIGIT[2]
- Novel ADCs,[3] e.g. datopotamab deruxtecan[4] and sacituzumab govitecan[5]

Novel strategies

- Cellular therapy, e.g. TIL and CAR T-cell therapy[2]
- Cancer vaccines, e.g. ATL001 and GRT-C901[6]

Key takeaways for ongoing research

- What other medications can be partnered with immunotherapy to improve efficacy in the first-line setting[7]
- ADCs are a key focus for research in the second-line setting, particularly understanding the biomarker directed/agnostic approach for patient selection[7]

EGFR-wildtype NSCLC: Key clinical trial data in the first line

Chemoimmunotherapy: 5-year outcomes

Phase III: **CheckMate 9LA**[8]
Nivolumab + ipilimumab + ChT vs ChT

- Nivolumab + ipilimumab + ChT **demonstrated continued OS benefit** vs ChT in all patients (HR 0.73; 95% CI 0.62–0.85)
- Clinical outcomes favoured triplet therapy vs ChT alone **across tumour PD-L1 expression and histology subgroups**
- **Higher incidence of grade 3 or 4 TRAEs** in the **triplet therapy group** vs ChT alone but these were consistent with prior reports; no new safety signals were identified

Phase III: **POSIEDON**[9]
Durvalumab + ChT ± tremelimumab vs durvalumab + ChT vs ChT

- Adding limited course tremelimumab to durvalumab + ChT **demonstrated durable long-term OS benefit** (HR 0.76; 95% CI 0.64–0.89)
- OS benefit observed **regardless of PD-L1 expression** but more pronounced in patients with NSQ vs SQ histology
- **Higher incidence of serious TRAEs** in the **triplet therapy group** vs doublet or ChT alone but extended follow-up revealed no new safety signals

Faculty and topics

Dr Aaron Lisberg presented the key clinical trial results for patients with *EGFR*-wildtype NSCLC in both the first- and second-line setting

Subgroup analysis[9]

OS benefit of tremelimumab + durvalumab + ChT maintained in hard-to-treat patients with NSQ *EGFR*/*ALK*-wildtype metastatic NSCLC with ***STK11* and/or *KEAP1* and/or *KRAS* mutations**

This patient population is being further explored in the ongoing phase IIIb **TRITON** trial[9]

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Novel agents for *EGFR*-wildtype NSCLC: Key clinical trial data in the first and second line

First-line

Phase III: HARMONi-2[10]
Ivonescimab vs pembro

Primary endpoint (PFS) met at preplanned interim analysis

mPFS (months)
Ivonescimab: 11
Pembrolizumab: 6
(HR 0.51; 95% CI 0.38–0.69)

PFS benefit of ivonescimab vs pembro broadly consistent across pre-specified subgroups*

Safety profile of ivonescimab consistent with prior studies and well tolerated

Phase II: EVOKE-02[5]
SG + pembro ± Pt-ChT

SG + pembro showed promising activity regardless of histology

ORR (%) NSQ population
PD-L1 TPS ≥50%: 67
PD-L1 TPS <50%: 37

ORR (%) SQ population
PD-L1 TPS ≥50%: 73
PD-L1 TPS <50%: 54

Median DoR not reached in either cohort

Safety profile manageable and consistent with known safety profile for each agent

Phase Ib: TROPION-Lung02[4]
Dato-DXd + pembro ± Pt-ChT

Dato-DXd + pembro ± Pt-ChT demonstrated durable antitumor activity regardless of PD-L1 expression

ORR (%) all patients
Doublet: 52 | Triplet: 56

ORR (%) PD-L1 TPS ≥50%
Doublet: 100 | Triplet: 53

ORR (%) PD-L1 TPS <50%
Doublet: 46 | Triplet: 56

Tolerability as expected for known safety profiles of each agent; no new safety signals observed

Second-line

Phase III: EVOKE-01[11]
SG vs docetaxel

Statistical significance not met but OS numerically improved with SG vs docetaxel across histologies

mOS (months)
SG: 11 | Docetaxel: 10

mPFS (months)
SG: 4 | Docetaxel: 4

ORR (%)
SG: 14 | Docetaxel: 18

Incidence of high-grade TEAEs and TEAEs leading to discontinuation were lower with SG than docetaxel

Phase III: TROPION-Lung01[12]
Dato-DXd vs docetaxel

Dato-DXd demonstrated clinically meaningful benefit vs docetaxel in NSQ NSCLC

Interim mOS (months)
Dato-DXd: 13 | Docetaxel: 11

mPFS (months)
Dato-DXd: 6 | Docetaxel: 4

ORR (%)
Dato-DXd: 31 | Docetaxel: 13

Safety profile manageable and consistent with the overall study population in TROPION-Lung01

Phase III:[13] Pragmatica-Lung[14]
Ramucirumab + pembro vs SoC

Ongoing registration-intent trial (follow-on from Lung-MAP S1800A)[14]

Eligible patients previously received PD-1/PD-L1 inhibitor therapy for ≥84 days and platinum-based therapy[14]

Primary outcome: OS[14]

Estimated enrolment: 700[14]

Primary completion: March 2025[13]

*SQ NSCLC, NSQ NSCLC, with TPS 1–49%, with liver metastases and with brain metastases.

EGFR-wildtype NSCLC: Clinical decision-making

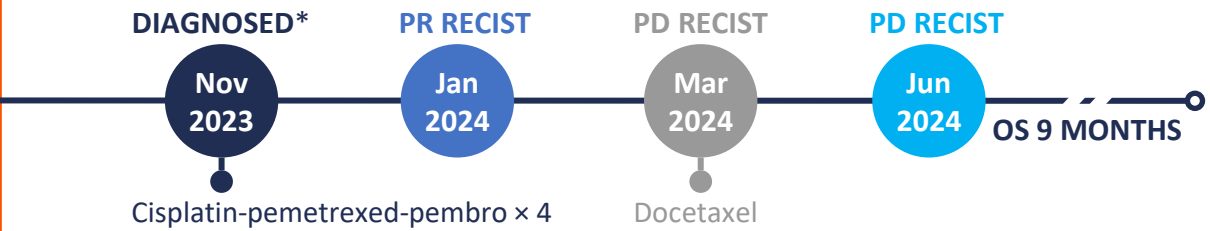
Evolving therapeutic options in advanced/metastatic *EGFR*-wildtype NSCLC

"There is much room for improving the prognosis of our patients affected by non-oncogene-addicted NSCLC. Docetaxel has long been unsurpassed in the post-chemoimmunotherapy setting, so let's hope the tsunami of ADCs will continue to bring new hope for the treatment of patients with NSCLC."

Tumour characteristics[15]
- Tumour burden
- Metastatic sites
- Histology
- PD-L1 expression
- Mutational status

Patient factors[15]
- Age, sex, PS
- Comorbidities
- Smoking status
- Patient preference

Treatment[15]
- Approved/reimbursed
- Number of cycles
- Tolerability/QoL
- Duration of response
- Oncologist's experience



Faculty and topics

Dr Sara Pilotto presented a clinical case and discussed the current treatment options, whilst highlighting the ongoing unmet medical needs

Key takeaways[15]

- **First-line treatment:** Based on tumour characteristics, patient factors and treatments approved/available via clinical trial
- **Second-line treatment:** Based on type of progression, patient factors, reliability of molecular profiling at baseline, treatments approved/available via clinical trial

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*Lung adenocarcinoma (cT4 N2 M1c, stage IVB [TNM 8th edition]; PD-L1-negative; *EGFR/ALK* wildtype; *KRAS*-, *STK11*- and *KEAP1*-mutant). Female, age 52 years, ECOG PS 1. †Maintenance.

Abbreviations and references

Abbreviations

ADC, antibody–drug conjugate; ALK, anaplastic lymphoma kinase; CAR, chimeric antigen receptor; ChT, chemotherapy; CI confidence interval; dato-DXd, datopotamab deruxtecan; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HR, hazard ratio; KEAP1, kelch like ECH associated protein; KRAS, Kirsten rat sarcoma viral oncogene homolog; LAG3, lymphocyte activation gene 3; m, median; NSCLC, non-small cell lung cancer; NSQ, non-squamous; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; pembro, pembrolizumab; PFS, progression-free survival; PR, partial response; PS, performance status; Pt-ChT, platinum-based chemotherapy; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumours; SG, sacituzumab govitecan; SoC, standard of care; SQ, squamous; STK11, serine/threonine kinase 11; TEAE, treatment-emergent adverse event; TIGIT, T cell immunoreceptor with Ig and ITIM domains; TIL, tumour-infiltrating T-lymphocyte; TPS, tumour proportion score; TRAE, treatment-related adverse event.

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