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

Clinical summary for Module 3: Bringing it together for optimal care

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Bringing it together: Novel strategies, care pathways and side-effect management

Oncology nurses are uniquely qualified to offer a wide range of support[1]

"In the MDT discussion it's important that everybody has some input, especially the nurses because they often know the patients best and they can explain what they feel the patient would be able to tolerate and what the patient's individual wishes are."

Faculty and topics

Jackie Fenemore presented key considerations for supporting patients with NSCLC through their treatment journey to improve outcomes and QoL

With treatment advances, patients are living longer, placing a growing emphasis on supportive care that preserves or improves patient QoL during and after active care[1]

Supportive care

- Adopt principles of prehabilitation to improve or maintain PS[2]
- Signpost to support groups and charities for emotional and physical help[1]

Supportive medication

- Provide prophylactic supportive medication,[3] e.g. antiemetics for nausea and vomiting; creams for skin reactions; medications for diarrhoea, pain and fatigue

Education

- Personalized patient education on when to contact the treating team about a potential side effect and encourage early reporting[4]
- Education for primary care physicians and local teams[5]

Communication

- Ensure patient's care team are kept abreast of any developments, e.g. local admission to hospital[6]
- Ensure good communication links, e.g. if side effects occur[6]

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Bringing it together: Implications of novel treatments on the shifting biomarker landscape

Biomarker testing driven by availability of targeted therapies[7]

"I think in the near future we will have to test for more, in particular more immunohistochemical markers, as ADCs will become more important and we will have to test for the targets of these ADCs, which are mainly protein markers that are on the cell surface or intracellular protein markers."

Faculty and topics

Prof. Dr Egbert Smit presented on the rationale, recommendations and challenges associated with biomarker testing in patients with NSCLC

ESMO[8] and NCCN[9] biomarker testing recommendations*

EGFR mutation	***NRG1*** fusion†
ALK rearrangement	***RET*** rearrangement
ROS1 rearrangement	***HER2*** mutation
BRAF ^{V600} mutation	***MET*** ex14 skipping
NTRK fusion	***MET*** amplification†
KRAS ^{G12C} mutation	**PD-L1** expression‡

Examples of emerging biomarkers

STK11 mutation[10]	**dMMR/MSI**[11]
KEAP1 mutation[10]	**TMB**[10]
HER2 amplification[10]	***TP53*** mutation[10]
BRAF non-V600 mutation[10]	***BRCA1/2*** mutation[10]
c-Met expression[10]	**TILs**[12]

NGS IHC FISH ISH

Quantitative immunofluorescence

ADC-related biomarkers

BIOMARKER GUIDED

T-DXd§[13] *HER2* mutation HER2-positive (IHC 3+)

T-DM1‖[14] *HER2* mutation

Teliso-V[15] c-Met over-expression

BIOMARKER AGNOSTIC

SG[16] TROP2

Dato-DXd[17] TROP2

HER3-DXd[18] HER3

*For advanced/metastatic NSCLC. †Recommended by ESMO only.[8] ‡ESMO recommends PD-L1 is systematically determined in advanced NSCLC;[8] NCCN recommends targeted therapy for the oncogenic driver takes precedence over treatment with an immune checkpoint inhibitor.[9] §FDA- and EMA-approved.[19,20] ‖Not approved but NCCN recommended.[9]

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Bringing it together: Optimizing outcomes in late-stage NSCLC: Key learnings

The importance of biomarker testing to guide treatment decisions

"Ultimately, we are going to need to identify biomarkers to help with risk-stratifying our patients to help us make these treatment decisions in the first-line setting. It becomes important because what we treat patients with in the first-line setting really dictates what treatment options are available in the second-line setting."

Faculty and topics

Dr Helena Yu, CD provided a summary of key learnings from across the three modules, as well as an update of recently presented data

1 *EGFR*-mutant NSCLC

- Osimertinib is the preferred **first-line** option[8,9]
  - Promising data in the first-line setting for approved combinations from FLAURA2[21] and MARIPOSA[22]
- **Second-line** treatment is based on resistance mechanisms (clinical trial),[8] SoC Pt-ChT or atez + bev + Pt-ChT[8] or amivantamab + ChT[9,23,24]
  - Promising data in the second-line setting from MARIPOSA-2,[25] HERTHENA-Lung01,[26] HERTHENA-Lung02,[27] HARMONi-A[28] and PALOMA-3[29]

2 *EGFR*-wildtype NSCLC

- ICI monotherapy is considered SoC[8] and is a preferred **first-line** option when PD-L1 TPS ≥50%*;[8,9] ICI + Pt-ChT preferred when PD-L1 TPS <50%†[8,9]
  - Promising long-term data in the first-line from CheckMate 9LA,[30] POSEIDON,[31] and EMPOWER-Lung 3;[32]
  - New data from HARMONi-2[33] and EVOKE-02[34]
- Options **after progression** on first-line therapy are limited[8,9,35]
  - Promising data using ADCs (e.g. EVOKE-01[36] and TROPION-Lung01)[37]

3 Bringing it together

- **Importance of the MDT** for optimizing care
  - Oncology nurses, as part of the wider MDT, can offer a wide range of support to patients, including prehabilitation, education, identification of AEs and managing side effects[1]
- **Importance of biomarker testing** to help guide treatment decisions
  - Shift towards large-panel NGS[10]
  - Potential for expanding the scope of IHC testing[38]

Outstanding practice gaps and future directions[39]

1. Biomarkers to help risk-stratify patients and improved treatment options for addressing CNS metastases
2. Second-line treatment options after disease progression on IO or chemo-IO
3. Universal comprehensive biomarker testing practices with better collaboration across medical disciplines

*Anti-PD-1/PD-L1; ICI + Pt-ChT is also a preferred option.[8,9] †ESMO recommends anti-PD-1/PD-L1 ± anti-CTLA-4 + Pt-doublet ChT followed by ICI ± pemetrexed or bev;[8] NCCN recommends Pt-doublet ChT + either pembro or cemiplimab as the preferred first-line options (additional recommended options include atez + bev + Pt-doublet ChT and anti-PD-1/PD-L1 + anti-CTLA-4 ± Pt-ChT, among others).[9]

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Bringing it together: Optimizing outcomes in late-stage NSCLC: Key data updates

EGFR-mutant NSCLC

Phase III: MARIPOSA[22]
Amivantamab + lazertinib vs osimertinib

First line

Amivantamab + lazertinib continued to show a trend towards improved OS vs osimertinib over a longer follow-up (vs interim OS analysis)

Median follow-up 31 months

mOS (months)
Amivantamab + lazertinib: NE
Osimertinib: 37
HR 0.77; 95% CI 0.61–0.96
p=0.019

61% of patients treated with amivantamab + lazertinib alive at 3 years vs 53% with osimertinib

Phase III: MARIPOSA-2[25]
Amivantamab + ChT vs ChT

After progression on osimertinib

OS did not reach prespecified significance threshold at the second interim OS analysis

Median follow-up 18 months

mOS (months)
Amivantamab + ChT: 18
ChT: 15
HR 0.73; 95% CI 0.54–0.99
p=0.039

Amivantamab + ChT significantly prolonged post-progression outcomes vs ChT

EGFR-wildtype NSCLC

Phase III: HARMONi-2[33]
Ivonescimab vs pembro

First line

PFS benefit of ivo vs pembro consistent across pre-specified groups* at a pre-planned interim analysis

Median follow-up 9 months

mPFS (months)
Ivonescimab: 11 | Pembro: 6

ORR (%)
Ivonescimab: 50 | Pembro: 39

Safety profile of ivonescimab consistent with prior studies and was well tolerated

Phase II: EVOKE-02[34]
SG + pembro + carboplatin

First line

Efficacy of SG seen across histology and PD-L1 subgroups

Median follow-up 14 months

mPFS (months)
SQ: 8 | NSQ: 8

PD-L1 TPS <1%: 8
PD-L1 TPS 1–49%: 7
PD-L1 TPS ≥50%: NR

Recommended dose for **SG: 7.5 mg/kg**
TEAEs manageable with appropriate supportive measures

Phase III: TROPION-Lung01[37]
Dato-DXd vs dtx

Previously treated patients

Second dual primary endpoint of OS showed a numerical improvement with Dato-DXd vs docetaxel

Median follow-up 23 months

mOS (months)
Dato-DXd: 13 | Dtx: 12

SQ
Dato-DXd: 8 | Dtx: 9

NSQ
Dato-DXd: 15 | Dtx: 12

Overall safety profile consistent with prior PFS data cutoff

*SQ, NSQ, PD-L1 TPS 1–49%, PD-L1 TPS ≥50%, with liver metastases, with brain metastases.

Abbreviations

ADC, antibody–drug conjugate; AE, adverse event; atez, atezolizumab; bev, bevacizumab; c-Met, cellular mesenchymal epithelial transition factor receptor; CD, course director; chemo-IO, chemoimmunotherapy; ChT, chemotherapy; CI, confidence interval; CNS, central nervous system; dato-DXd, datopotamab deruxtecan; dMMR, mismatch repair deficient; dtx, docetaxel; EGFR, epidermal growth factor receptor; ESMO, European Society for Medical Oncology; ex14, exon 14; FISH, fluorescence *in situ* hybridization; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor receptor 3; HER3-DXd, patritumab deruxtecan; HR, hazard ratio; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; IO, immunotherapy; ISH, *in situ* hybridization; MDT multidisciplinary team; MET, mesenchymal epithelial transition factor receptor; m, median; MSI, microsatellite instability; NCCN, National Comprehensive Cancer Network®; NE, not evaluable; NGS, next-generation sequencing; NR, not reached; NSCLC, non-small cell lung cancer; NSQ, non-squamous; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand-1; pembro, pembrolizumab; PFS, progression-free survival; PS, performance status; Pt-ChT, platinum-based chemotherapy; QoL, quality of life; SG, sacituzumab govitecan; SoC, standard of care; SQ, squamous; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; teliso-V, telisotuzumab vedotin; TIL, tumour infiltrating lymphocyte; TMB, tumour mutational burden; TPS, tumour proportion score; TROP2, trophoblast cell-surface antigen 2.

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