

CLINICAL FLASHCARDS

Targeted ADCs For Advanced Lung Cancer

The Life Science Feed

QUESTION

What three components define the structure of an antibody-drug conjugate (ADC)?

ANSWER

A monoclonal antibody, a potent cytotoxic payload, and a chemical linker.

QUESTION

What is the primary mechanism of action for an ADC in cancer treatment?

ANSWER

The antibody delivers a cytotoxic payload directly to tumour cells expressing a specific antigen, sparing normal tissue.

QUESTION

How does the "bystander effect" enhance the efficacy of third-generation ADCs in heterogeneous tumours?

ANSWER

The membrane-permeable payload is released intratumorally and diffuses to kill neighbouring tumour cells that do not express the target antigen.

QUESTION

Which specific payload is used in trastuzumab deruxtecan (T-DXd)?

ANSWER

DXd, which is a topoisomerase I inhibitor.

QUESTION

How does the drug-to-antibody ratio (DAR) of trastuzumab deruxtecan (T-DXd) compare to earlier ADCs?

ANSWER

It has a higher ratio of approximately 8 molecules per antibody, compared to 3 or 4 in earlier agents.

QUESTION

Why is the bystander effect particularly important for treating non-small cell lung cancer (NSCLC)?

ANSWER

NSCLC tumours are heterogeneous, meaning not every cell expresses the target antigen at the same level.

QUESTION

What is the traditional second-line chemotherapy anchor that ADCs are intended to replace in NSCLC?

ANSWER

Docetaxel or docetaxel-based combinations.

QUESTION

In NSCLC, what is the specific actionable biomarker for trastuzumab deruxtecan (T-DXd) therapy?

ANSWER

HER2 exon 20 insertion mutations.

QUESTION

Approximately what percentage of NSCLC adenocarcinomas harbour HER2 exon 20 insertions?

ANSWER

Between 2% and 3%.

QUESTION

How does HER2 status relevance differ between breast cancer and NSCLC for ADC targeting?

ANSWER

In NSCLC, the target is defined by mutation rather than the HER2 protein overexpression typical in breast cancer.

QUESTION

What response rate was reported for the HER2-mutant cohort in the DESTINY-Lung01 trial?

ANSWER

A response rate of 55%.

QUESTION

What was the median progression-free survival (PFS) for HER2-mutant patients in the DESTINY-Lung01 trial?

ANSWER

8.2 months.

QUESTION

In the DESTINY-Lung02 trial, what was the confirmed median overall survival (OS) for patients receiving the 5.4 mg/kg dose?

ANSWER

19.5 months.

QUESTION

What is the current standard of care for HER2-mutant NSCLC following progression on platinum-based therapy?

ANSWER

Trastuzumab deruxtecan (T-DXd).

QUESTION

Which transmembrane glycoprotein is the target for the ADC datopotamab deruxtecan (dato-DXd)?

ANSWER

TROP2 (trophoblast cell-surface antigen 2).

QUESTION

In the TROPION-Lung01 trial, what was the hazard ratio (HR) for progression-free survival when comparing dato-DXd to docetaxel?

ANSWER

The hazard ratio was 0.75.

QUESTION

Which subgroup in TROPION-Lung01 appeared to derive the most significant benefit from dato-DXd?



ANSWER

The non-squamous, non-driver-mutated subgroup.

QUESTION

What is the clinical significance of HER3 (ErbB3) expression in NSCLC?

ANSWER

It is expressed at high levels in the majority of NSCLC tumours, including those with EGFR or ALK alterations.

QUESTION

Which ADC has shown promise for EGFR-mutant NSCLC after progression on osimertinib?

ANSWER

Patritumab deruxtecan (HER3-DXd).

QUESTION

What were the response rate and median PFS reported in the HERTHENA-Lung01 trial for HER3-DXd?

ANSWER

A response rate of 29.8% and a median PFS of 5.5 months.

QUESTION

What is considered the most serious toxicity associated with DXd-payload ADCs?



ANSWER

Interstitial lung disease (ILD).

QUESTION

In the DESTINY-Lung02 trial, what was the incidence rate of ILD at the 5.4 mg/kg dose of T-DXd?

ANSWER

12.4% of patients, with 2.3% being grade 5 (fatal).

QUESTION

What are the common clinical presentations of ADC-induced ILD?

ANSWER

New or worsening dyspnoea, cough, and ground-glass opacities on CT scan.

QUESTION

What is the management step for Grade 1 (asymptomatic) T-DXd-induced ILD?

ANSWER

Withhold T-DXd and monitor the patient closely.

QUESTION

What is the required management for Grade 2 (symptomatic) ADC-induced ILD?

ANSWER

Hold the ADC and initiate corticosteroids at ≥ 0.5 mg/kg/day with a slow taper over at least 4 to 6 weeks.

QUESTION

What is the protocol for patients who develop Grade 3 or higher ADC-induced ILD?

ANSWER

Permanently discontinue the ADC and initiate high-dose corticosteroids.

QUESTION

Which ADC targets are specifically linked to a higher incidence of ocular toxicities like conjunctivitis and keratitis?

ANSWER

TROP2-targeting ADCs, such as dato-DXd and sacituzumab govitecan.

QUESTION

What prophylactic measure is recommended to manage ocular toxicity in patients receiving TROP2 ADCs?

ANSWER

Prophylactic steroid eye drops.

QUESTION

What are the common haematological toxicities associated with the ADC class?



ANSWER

Neutropenia and anaemia.

QUESTION

Why is baseline pulmonary function testing and CT imaging essential before starting ADC therapy?

ANSWER

To establish a baseline and identify patients with significant pre-existing ILD who are at higher risk.

QUESTION

Which emerging ADC targets in NSCLC are currently in early clinical development?



ANSWER

MET and CEACAM5.

QUESTION

How should nausea be managed in patients starting their first cycles of ADC therapy?

ANSWER

With standard prophylactic antiemetics.

QUESTION

The ability of an ADC to kill nearby cells regardless of their antigen expression level is known as the _____.

ANSWER

Bystander effect

QUESTION

In the TROPION-Lung01 trial, dato-DXd demonstrated superiority over _____ in previously treated advanced NSCLC.

ANSWER

Docetaxel

QUESTION

The primary clinical indication for T-DXd in NSCLC requires the presence of a _____ mutation.

ANSWER

HER2 (or ERBB2)

QUESTION

Concept: DAR

ANSWER

Definition: Drug-to-Antibody Ratio; the average number of cytotoxic payload molecules attached to each monoclonal antibody.

QUESTION

Concept: Grade 2 ILD

ANSWER

Definition: Symptomatic interstitial lung disease that requires medical intervention (steroids) and interruption of the causative drug.

QUESTION

Why is comprehensive molecular testing essential for the use of ADCs in NSCLC?

ANSWER

It identifies HER2 mutation status, which is necessary to qualify patients for T-DXd treatment.

QUESTION

What potential resistance issue arises when sequencing multiple ADCs in one patient?



ANSWER

Cross-resistance caused by shared cytotoxic payloads.

QUESTION

How does T-DXd payload release differ from earlier generations?

ANSWER

It uses a cleavable linker that releases the payload intratumorally, rather than requiring internalisation in every target cell.

QUESTION

What trial is investigating the first-line use of dato-DXd plus pembrolizumab in non-squamous NSCLC?



ANSWER

TROPION-Lung08.

QUESTION

What was the median progression-free survival (PFS) for docetaxel in the TROPION-Lung01 trial?

ANSWER

3.7 months.

QUESTION

In NSCLC patients, what common conditions must be differentiated from drug-induced ILD?

ANSWER

Disease progression, infection, and pulmonary embolism.

QUESTION

The trial evaluating patritumab deruxtecan in EGFR-mutated NSCLC is named _____.

ANSWER

HERTHENA-Lung01

QUESTION

What is the typical duration for tapering corticosteroids after Grade 2 ADC-induced ILD?

ANSWER

At least 4 to 6 weeks.

QUESTION

Which generation of ADCs is trastuzumab deruxtecan considered to be?

ANSWER

Third-generation.

QUESTION

In the HERTHENA-Lung01 trial, what specific previous treatment had all patients progressed on?



ANSWER

A third-generation TKI (typically osimertinib).

QUESTION

Why were patients with prior immunotherapy-induced ILD generally excluded from ADC clinical trials?

ANSWER

Due to the high risk of severe or fatal pulmonary toxicity when treated with DXd-payload agents.

QUESTION

What was the reported median PFS for dato-DXd in the TROPION-Lung01 trial?

ANSWER

4.4 months.

QUESTION

How does the ubiquity of HER3 expression affect its potential as an ADC target?

ANSWER

It makes it a potentially broad target across various NSCLC subtypes, including those with different driver mutations.