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Evaluating second-line treatment approaches in advanced NSCLC: The role of ADCs

Practice aid for the treatment of NSCLC

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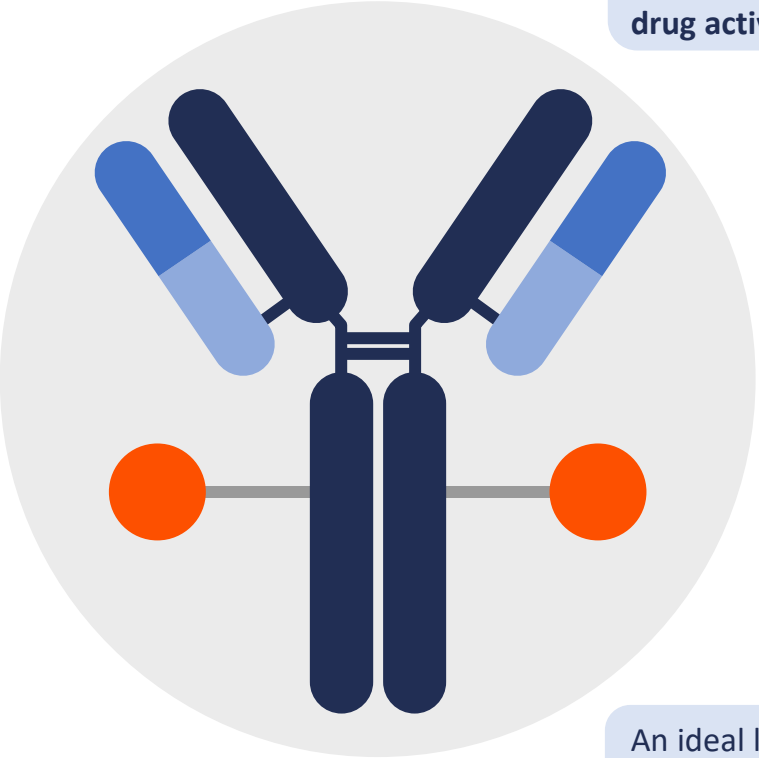
Linking ADC structure with efficacy and toxicity



In addition to the anti-tumour activity of the cytotoxic payload, **monoclonal antibodies** can possess **direct** anti-tumour activity,[1,2] e.g. trastuzumab blocks signalling of tumour antigens associated with cell function and multiplication,[2] and **indirect** anti-tumour activity via immune mediated cytotoxicity, e.g. antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.[1,2] ADCs therefore **combine antibody and cytotoxic drug activities** to provide various modes of action.[3]

The **DAR** is the average number of payload moieties attached to each monoclonal antibody,[4] which has important efficacy and safety implications.[1] A **low DAR** may have limited clinical efficacy, but a **high DAR** can result in increased plasma concentration and high rates of non-specific uptake (e.g. in the liver), leading to off-target toxicity.[1,5]

Some ADCs can exert indirect anti-tumour activity through the **bystander effect**,[1] where the cytotoxic payload diffuses through the membrane to the neighbouring cells within the local tumour environment.[5] The ability of an ADC to exert the bystander effect depends on factors such as physiochemical characteristics of the cytotoxic payload and type of linker.[1] As well as **amplifying the anti-tumour potency** of an ADC, the bystander effect can also **exacerbate off-target toxicities** due to increased distribution of the cytotoxic payload in healthy tissues.[5]

An ideal linker is stable in the systemic circulation and deconjugates in the target tumour cell.[6] **Poor linker stability** can lead to **premature release of the cytotoxic payload** in the systemic circulation and **increased off-site toxicity** relative to on-site toxicity.[5]

ADC safety: Potential class effects irrespective of antigen target

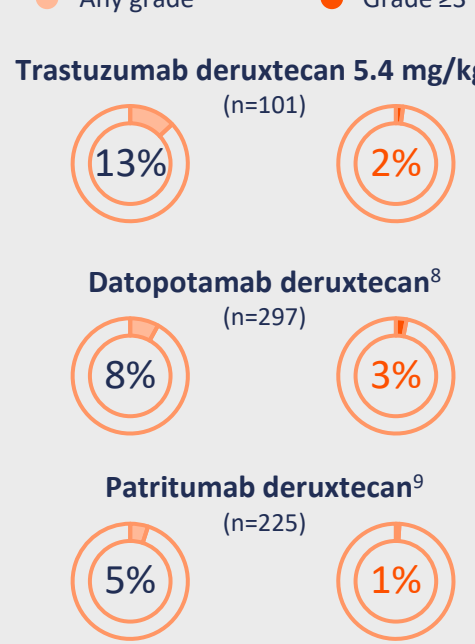
Microtubule inhibitors[4,5]

- **Auristatin**[4]
  - **MMAE; vedotin**[5]
    Anaemia; neutropenia; peripheral neuropathy, skin toxicity
  - **MMAF; mafodotin**[5]
    Ocular toxicity, thrombocytopenia, hepatic toxicity
- **Maytansinoid**[4]
  - **DM1; emtansine**[5]
    Thrombocytopenia; hepatic toxicity
  - **DM4; soravtansine**[5]
    Ocular toxicity, neutropenia, anaemia, peripheral neuropathy

Topoisomerase inhibitors[4,5]

- **Camptothecin**[4]
  - **Deruxtecan**[4,5]
    Pulmonary toxicity; neutropenia, gastrointestinal toxicity
  - **Govitecan**[5]
    Neutropenia; diarrhoea

Frequency of ILD in phase II/III clinical trials of patients with advanced NSCLC



Toxicities are not always predictable[4]

Two ADCs with the same payload, linker and similar DARs can have different toxicity profiles, and two ADCs with different payloads can cause the same toxicity

Consideration of ADC toxicity profiles is required, along with the use of strategies to minimize the risk and impact of ILD

Direct comparisons between trials should not be made due to differences in trial design.

*Approved dose.[10,11]

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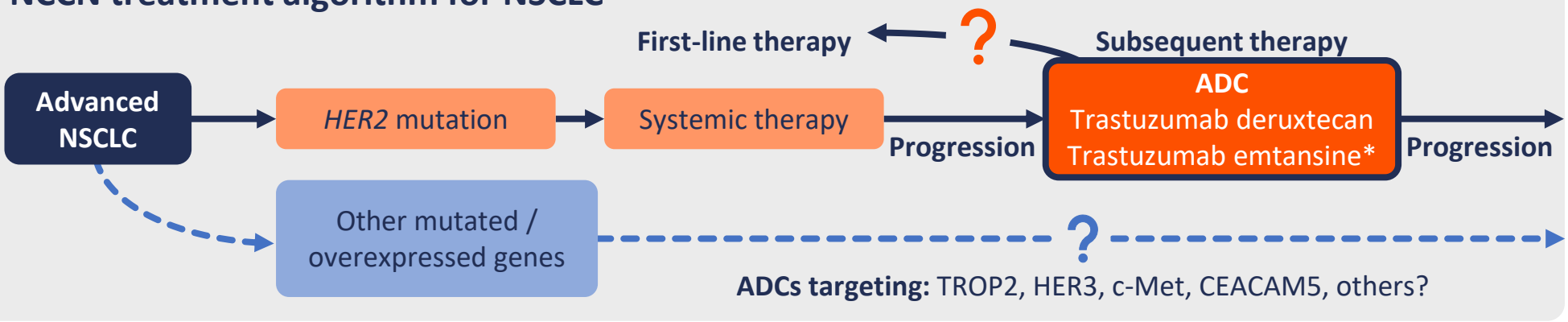
Integrating ADCs into the advanced NSCLC treatment paradigm

NCCN treatment algorithm for NSCLC[12]



ADC	Target antigen	Prevalence in patients with NSCLC	Biomarker assessment	Evidence for a biomarker-guided approach	Supporting trial(s)
Trastuzumab deruxtecan[7,13,14]	*HER2* mutation[7,13]	1–4%[15]	NGS[7,13]	✓[7,13]	DESTINY-Lung01[13,14] DESTINY-Lung02[7]
	HER2 overexpression[13,14]	2–30%[15]	IHC[13,14]	✓[14]	
	HER2 amplification[7,13]	2–5%[15]	NGS[13]	?[7,13]	
Sacituzumab govitecan[16]	TROP2 expression[8,16–18]	64%†[19]	IHC[16,17]	✗[16,17]	IMMU-132-01[16]
Datopotamab deruxtecan[8,17,18]					TROPION-PanTumor01[17] TROPION-Lung05[18] TROPION-Lung01[8]
Patritumab deruxtecan[9]	HER3 expression[9,20]	42%[21]	IHC[9,20]	✗[9,20]	HERTHENA-Lung01[9]
Telisotuzumab vedotin[22]	c-Met overexpression[22]	25–39%[23]	IHC[22]	✓[24]	LUMINOSITY[22]
Tusamitamab ravtansine‡[25,26]	CEACAM5 expression[25]	25%§[27]	IHC[25]	✓[25]	NCT02187848[25,26]

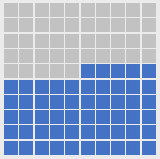
*NCCN recommended but not FDA approved. †Adenocarcinomas. ‡The global clinical development program for tusamitamab ravtansine in patients with NSCLC has been discontinued.[28] §Non-squamous NSCLC.

Evidence for the use of biomarkers in ADC treatment selection

Trastuzumab deruxtecan, telisotuzumab vedotin and tusamitamab ravtansine: Evidence for a biomarker-guided approach

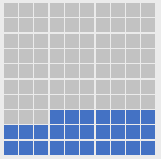
Trastuzumab deruxtecan[13]
6.4 mg/kg (N=91)

***HER2* mutant**
ORR
55%



Trastuzumab deruxtecan[14]
6.4 mg/kg (n=49)

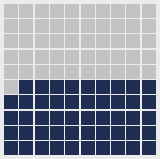
HER2 overexpressing
ORR
27%



Recommended dose: 5.4 mg/kg[10,11]

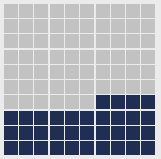
Trastuzumab deruxtecan[7]
5.4 mg/kg* (n=102)

***HER2* mutant**
ORR
49%



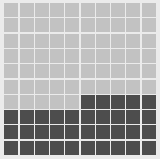
Trastuzumab deruxtecan[14]
5.4 mg/kg* (n=41)

HER2 overexpressing
ORR
34%

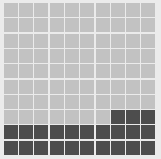


Telisotuzumab vedotin[22,24]
1.9 mg/kg (patient numbers not reported)

c-Met high
ORR
35%[24]

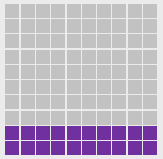


c-Met intermediate
ORR
23%[24]

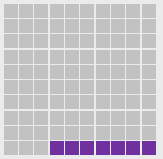


Tusamitamab ravtansine[25] 100 mg/m²

CEACAM5 high
(n=64)
ORR
20%



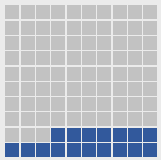
CEACAM5 moderate
(n=28)
ORR
7%



Sacituzumab govitecan and patritumab deruxtecan: Evidence for a biomarker-agnostic approach

Sacituzumab govitecan[16]
8 mg/kg or 10 mg/kg (N=54)

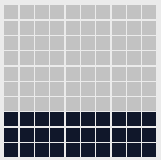
ORR
17%



- No preselection on the basis of TROP2 expression
- High TROP2 expression in most epithelial cancers means its utility as a biomarker for sacituzumab govitecan patient selection is doubtful

Patritumab deruxtecan[9]
5.6 mg/kg (n=225)

ORR
30%



- No preselection for HER3 expression
- Responses observed across the range of pretreatment tumour HER3 membrane expression

Direct comparisons between trials should not be made due to differences in trial design.
*Approved dose.[10,11]

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Abbreviations and references

Abbreviations

ADC, antibody–drug conjugate; CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; c-Met, mesenchymal epithelial transition factor; DAR, drug–antibody ratio; DM1, N_2'-deacetyl-N_2'-(3-mercapto-1-oxopropyl)-maytansine; DM4, N_2'-deacetyl-N_2'-(4-mercapto-4-methyl-1-oxopentyl)-maytansine; FDA, US Food and Drug Administration; HER2/3, human epidermal growth factor receptor 2/3; IHC, immunohistochemistry; ILD, intersitial lung disease; MMAE/F, monomethyl auristatin E/F; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; ORR, objective response rate; TROP2, trophoblast cell surface antigen.

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