Lung Cancer xxx (xxxx) 109507

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Review article

New biomarkers for antibody-drug conjugates in lung cancer the pathologist's perspective

Véronique Hofman [a, b, *], Guylène Rignol [a, b], Baharia Mograbi [a, b], Marius Ilié [a, b], Mariona Riudavets [c], Fernando Lopez-Rios [d], Nicola Fusco [e, f], Umberto Malapelle [g], Sanjay Popat [h], Albrecht Stenzinger [i], David Planchard [j], Antonio Passaro [k], Simon Heeke [l], Solange Peters [m], Ignacio Ivan Wistuba [n], Fred R. Hirsch [o], Paul Hofman [a, b]

[a] IHU RespirERA, FHU OncoAge, Côte d'Azur University, Laboratory of Clinical and Experimental Pathology, Biobank BB-0033-00025, Pasteur Hospital, Nice, France
[b] IRCAN, Inserm U1081, Faculty of Medicine, Nice, France
[c] Department of Thoracic Oncology, Hôpital Cochin APHP Centre, Paris, France
[d] Department of Pathology, Research Institute, Hospital Universitario 12 de Octubre, Universidad Complutense de Madrid, (imas12), CIBERONC, Madrid, Spain
[e] Division of Pathology, European Institute of Oncology IRCCS, Milan, Italy
[f] Department of Oncology and Hemato-Oncology, University of Milan, Italy
[g] Department of Public Health, University of Naples Federico II, Naples, Italy
[h] Royal Marsden Hospital and Institute of Cancer Research, London, United Kingdom
[i] Institute of Pathology Heidelberg (IPH), Center for Molecular Pathology, University Hospital Heidelberg and Translational Lung Research Center Heidelberg (TLRC-H), Member of the German Center for Lung Research (DZL), Heidelberg, Germany
[j] Department of Cancer Medicine, Gustave Roussy Cancer Campus, Villejuif, France
[k] Division of Thoracic Oncology, European Institute of Oncology, IRCCS, Milan, Italy
[l] Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[m] Department of Oncology, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland
[n] Department of Translational Molecular Pathology, Moffitt Hospital, Tampa, FL, USA
[o] Center for Thoracic Oncology, Tisch Cancer Center, Icahn School of Medicine, Mount Sinai Hospital, NY, USA

ARTICLE INFO

Keywords:
Antibody-drug conjugates
Lung cancer
Biomarkers
Immunohistochemistry
Molecular biology
Limitations

ABSTRACT

Antibody-drug conjugates (ADC) as a new treatment modality have enabled novel, promising treatment options in lung cancer. However, biomarkers for the selection of appropriate treatments are still under development, posing novel challenges for tissue selection and development of companion diagnostics (CDx). In this review, we address the challenges and discuss best practice for fast, reliable and robust implementation of novel biomarkers in treatment selection of ADCs in lung cancer.

1. Introduction

The epidemiology and prognoses for lung cancer patients have evolved in the past two decades [1–5], with *i*) an increased incidence of non-small cell lung cancer (NSCLC) in never-smokers and younger patients, and *ii*) considerably improved survival of NSCLC patients in developed countries, independent of disease stage. Screening programs for lung cancer and early tumor detection have contributed, but so too the shift in the therapeutic landscape, with the impact of targeted therapies, immunotherapies and improvements in surgery and chemo-radiotherapy [6–8]. The recent development of antibody-drug conjugates (ADCs) [9–16] combines target specificity of monoclonal antibodies with cytotoxic or immuno-stimulatory payloads [14] and opens up promising alternative strategies for both first- and second-line lung cancer treatment, either alone or in combination with other treatments [17–19].

The activity of ADCs varies between lung cancer patients [16,20], hence predictive biomarkers would benefit selection of patients who may be eligible for specific ADCs, while other ADCs are currently administered independent of any identified biological target [20–22]. Some clinical trials, but not all, require companion diagnostic testing (CDx), by molecular or immunohistochemical (IHC) methods, before

* Corresponding author at: IHU RespirERA, Pasteur Hospital, University Côte d'Azur, 30 Avenue de la Voie Romaine, 06000 Nice, France.
E-mail address: hofman.p@ihu-respirera.fr (V. Hofman).

https://doi.org/10.1016/j.lungcan.2026.109507
Received 15 June 2026; Accepted 22 June 2026
0169-5002/

ADC delivery [20]. Thus, assessment and integration of new CDx into daily practice presents a new challenge for thoracic pathologists [23, 24], principally assessment of all mandatory predictive biomarkers needed for correct treatment decision making, according to the sample tissue size, the percentage of tumor cells, and/or the potential cytological specimen [25–27].

This review addresses current and emerging biomarkers to identify strategies for the use of ADC in thoracic oncology. New challenges and issues that thoracic pathologists will face due to rapid implementation of new biomarkers into daily practice are discussed and potential new approaches to bridge existing gaps in the development of multiple CDx-associated ADCs are presented.

1.1. Mechanisms of action and main targets of antibody-drug-conjugates for lung cancer

1.1.1. Structure and mechanisms of action

The structure and mechanisms of action of ADCs have been extensively reviewed elsewhere [14,28,29]. In brief, an ADC comprises a monoclonal antibody, a linker and a cytotoxic payload [14]. Following antibody binding, the antigen-ADC complex must be internalized to enable intracellular payload release. Optimal targeting requires antigen expression at the tumor cell surface, with minimal expression in normal tissue to limit off-target toxicity, high antigen–antibody affinity, ready internalisation and long plasma half-life. [29,30].

The linker may be cleavable or not. Non-cleavable linkers have high plasma stability and favorable tolerance. Cleavable linkers predominate among next generation ADCs and are chemically or enzymatically cleaved intracellularly. Once internalized, the ADC-antigen complex in endosomes fuses with lysosomes, allowing release of the cytotoxic payload [14,30] (Fig. 1). Lipophilic payloads can diffuse across cell membranes, generating a bystander effect that enhances activity against neighboring tumor cells and the tumor microenvironment, a key advantage in heterogenous tumors.

Recent technological advances define third-generations of ADCs, feature more stable linkers, more precise conjugation, improved homogeneity of the drug-antibody ratio (DAR), more specific target binding (e.g. bispecific antibodies) and an enhanced therapeutic index [30]. However, multiple resistance mechanisms to ADCs have been increasingly reported [31,32] affecting each step of the pathway, thus continued development of ADC engineering is needed: e.g. linkers that are too stable may not cleave after internalization, preventing cytotoxic payload release so tumor–killing activity drops dramatically. Increased ADC doses to overcome this issue can increase systemic exposure to the antibody–linked toxin without extra benefit and the contact time with normal tissues is prolonged, potentially worsening on–target/off–tumor effects.

1.1.2. Main targets for lung cancer treatment

Most of the growing number of ADCs are still in pre-clinical or early-stage development, with only a few evaluated in clinical trials to date. Some ADCs have been recently approved by the US Food and Drug Administration (FDA) including trastuzumab-deruxtecan (T-DXd) for *HER-2* mutated NSCLC, telisotuzumab-vedotin (Teliso-V) in MET overexpression and datopotamab-DXd (Dato-DXd) in *EGFR* mutated NSCLC [13]. The main protein targets are described below and listed in Table 1 for both NSCLC and small cell lung cancer (SCLC). It is important to distinguish the current ADCs for which biomarker assessment is mandatory (e.g. c-MET expression, *EGFR* mutations and HER2 expression or mutation) from those for which assessment is uncertain at present (e.g. TROP2 expression), or those where the identification of predictive biomarkers remains uncertain or has failed [20]. ADCs targeting HER3, DLL3, B7-H3, CEACAM 5, integrin β6 and SEZ6 do not currently correlate with any biomarker [20,33], but many are under investigation (Table 1).

1.1.3. ADC targets for non-small cell lung cancer

ADCs are in development across diverse targets and settings in NSCLC. The approval in 2022 of T-DXd for *HER2*-mutant NSCLC marked a critical milestone in this area, establishing ADCs as a treatment modality in thoracic oncology [34]. The main ADCs approved or in development for NSCLC are as follows:

- *c-MET*

c-MET expression, detected by IHC, is one of the most extensively investigated biomarkers for ADC-based strategies in NSCLC [35–39]. Its dysregulation includes overexpression, gene amplification and exon 14-skipping mutations. Overexpression of c-MET is a clinically relevant and therapeutically actionable biomarker for ADC-based approaches, such as Teliso-V [37]. In the LUMINOSITY trial, advanced non-squamous NSCLC *EGFR* wild-type tumors with high c-MET protein

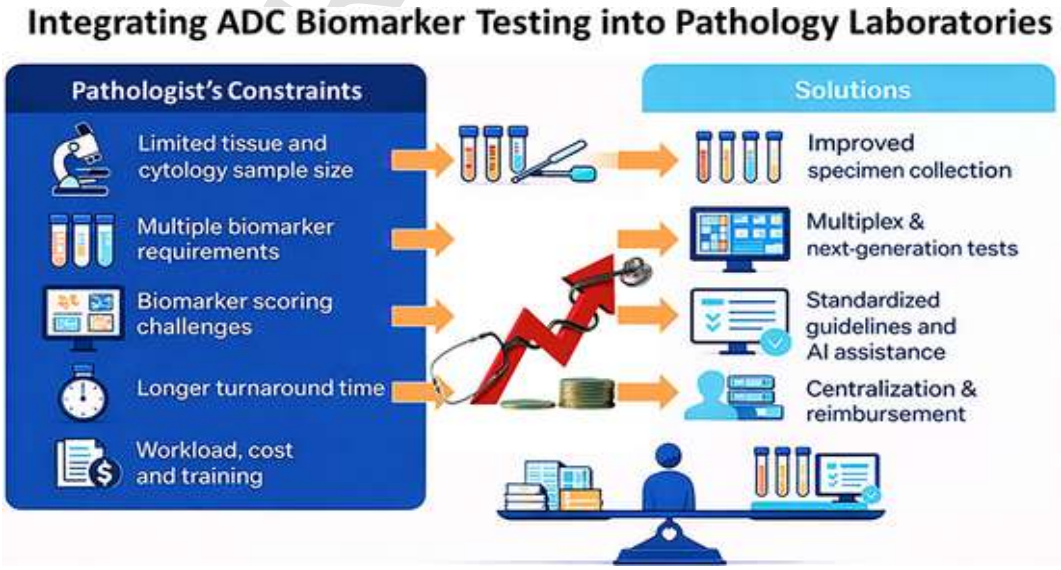

Fig. 1. Constraints facing thoracic pathologists for integrating antibody-drug conjugate biomarker testing and potential solutions.

Table 1
Main targets identified by immunohistochemistry for antibody-drug conjugate in non-small cell and small-cell lung carcinoma.

Lung cancer biomarker for ADC – IHC assessment current status*				
Lung carcinoma histological type	Most current biomarker	IHC validated as a CDx	Ongoing biomarkers assessment by IHC	Currently not listed as IHC biomarkers
Non-Small Cell Lung Cancer (NSCLC)	**HER2**	✓		
	C-MET	Not	✓ Cutoff > 50% with 3 + intensity Cutoff > 90% with 3 + intensity	
	TROP2	Not	✓ NMR QCS scoring system	
	CEACAM5	Not	✓	
	HER3	Not	Not	✓
	B7-H3	Not	Not	✓
	Nectin 4	Not	Not	
Small Cell Lung Cancer (SCLC)	**SEZ6**	Not	✓	
	B7-H3		✓	
	Integrin β6		✓	
	DLL3		Not	✓
	TROP2			

Abbreviations:
- CDx: Companion Diagnostics Test.
- IHC: Immunohistochemistry.
- NMR QCS.
- HER2: Human Epidermal Growth Factor Receptor 2.
- C-MET: Mesenchymal-Epithelial Transition Factor.
- TROP2: Trophoblast Cell Surface Antigen 2.
- CEACAM5: Carcinoembryonic Antigen-Related Cell Adhesion Molecule 5.
- HER3: Human Epidermal Growth Factor Receptor 3.
- B7-H3: CD276.
- SEZ6: Seizure Related 6 Homolog.
- DLL3: Delta-Like Ligand 3.

*__Note:__ The validation status and clinical utility of these biomarkers may evolve as new clinical trial data becomes available. Always refer to current guidelines (ESMO, NCCN, CAP) and FDA/EMA approvals for the most up-to-date recommendations.

overexpression (defined as superior or equal to 50% of tumor cells showing strong (3 +) staining) responded best to Teliso-V [37]. In 2025, the FDA granted accelerated approval for Teliso-V in patients with previously-treated non-squamous NSCLC, determined by an FDA-approved CDx [40]. Access to Teliso-V in Europe requires confirmation of its efficacy for c-MET-positive patients: a phase III study (TeliMET NSCLC-01 study) *vs* docetaxel is currently in progress. Other clinical trials showed promising results in patients with *EGFR* wild-type or *EGFR* mutated tumors expressing high levels of c-MET protein [37]. Several other c-MET-targeting ADCs, including ABBV-400, REGN5093-M114, and AZD9592, are in development. Notably, some clinical trials, such as those using ABBV-400, are based on *MET* gene amplification as well as overexpression. Proposed variable thresholds for different staining intensity and percentage of tumor cells will likely be evaluated for various drugs being developed to target c-MET. Examples of c-MET IHC are shown in Supplementary Fig. 1.

- *HER2*

Initial development of HER2-directed ADCs in NSCLC was restricted to tumors with *HER2* mutations [41,42], with *HER2* exon 20 mutations as the most clinically established biomarker for HER2-directed ADCs [4,43–51]. Data showing activity of drugs against any *HER2* activating mutation, kinase or non-kinase, led to FDA and European Medicines Agency (EMA) approval of those drugs. Early clinical trials demonstrated that *HER2* mutations better predicted response to the ADCs trastuzumab-emtansine and T-DXd than HER2 overexpression and amplification [42–46,50–52]. Thus, although HER2 IHC is FDA approved as a biomarker test for tumor-agnostic ADC, its use for HER2 overexpression and amplification requires further study [50,52]. In 2024, T-DXd was granted approval by the FDA for use in patients in the USA with unresectable or metastatic HER2 NSCLC (IHC score 3 +), who have received prior systemic treatment and have no alternative treatment options [53].The EMA has not approved this use and a confirmatory trial may be requested [52]. Examples of HER2 IHC are shown in Supplementary Fig. 2.

- *TROP2*

Trophoblast cell surface antigen-2 (TROP2) is a transmembrane glycoprotein involved in cellular proliferation and is broadly expressed in NSCLC [54,55]. TROP2- directed ADCs are under development, sparking interest in biomarker-informed patient selection [56,57]. Dato-DXd is an anti-TROP2 ADC conjugated to deruxtecan, a topoisomerase 1 inhibitor. In the phase 3 TROPION-Lung01 trial, Dato-DXd improved progression free survival (PFS) in previously treated, advanced non-squamous NSCLC [58] but did not improve overall survival compared to docetaxel and no improvement in squamous cell carcinomas was observed. Post-hoc analysis indicated improvement occurred in the cohort with mutations in *EGFR*. Furthermore, in the phase 2 TROPION-Lung05 trial of relapsed advanced non-squamous NSCLC, with an associated genomic alteration, efficacy occurred independently in the *EGFR* mutated subset. As a result of blended analysis of these post-hoc data, FDA approval was granted in 2025 for Dato-DXd for patients with *EGFR* mutation [59,60]. Confirmatory randomized phase 3 trials are in progress. Dato-DXd is currently being trialed as first-line treatment of metastatic wildtype NSCLC, in combination with pembrolizumab, or durvalumab plus pemetrexed, with or without carboplatin. It is also being trialed for resectable NSCLC [61]. Another anti-TROP2 ADC, sacituzumab-tirumotecan, developed in China for NSCLC patients with *EGFR* mutation, in the second or third-line setting, showed positive results over chemotherapy in two randomized trials and has been approved for use in China and the USA [62,63].Note that clinical trials targeting TROP2 may or may not use specific tools for TROP2 expression, such as the Normalized Membrane Ratio Quantitative Continuous Scoring (NMR QCS) (see below). Examples of TROP2 IHC are shown in Supplementary Fig. 3.

- *HER3*

HER3 is expressed in NSCLC and became a promising target, particularly for tumors bearing *EGFR*-mutations [64,65]. Patritumab-deruxtecan (HER3-DXd) is an anti-HER3 antibody conjugated to a topoisomerase 1 inhibitor. In the phase 2 HERTHENA-Lung01 trial, response to HER3-DXd occurred independently of the level of HER3 expression, including the H-score [66]. Although HER3-DXd demonstrated efficacy after failure of EGFR tyrosine kinase inhibitors, regardless of the HER3 IHC status, the HERTHENA-Lung03 trial was discontinued in 2025, after the HERTHENA-Lung02 failed to show improvement in overall survival.

- *Other Potential ADC Targets*

Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) protein expression was tested as a target for ADCs [67–69]. However, in clinical trials, no overall survival benefit was observed and with limited efficacy, tusamitamab-ravtansine was not pursued for NSCLC [70]. Of note, the biomarker design, which required 2 + posi-

tivity in at least 50% of tumor cells, may not have been valid and might have contributed to the negative outcome of the phase 3 CARMEN-LC03 clinical trial.

In addition to HER2, alternative cell surface targets for ADCs in NSCLC include the immune checkpoint molecule B7-H3 (CD276), which is expressed across multiple solid malignancies including NSCLC and whose overexpression has been consistently associated with poor prognosis, aggressive tumor biology and adverse clinical outcomes [71]. B7-H3 is implicated in immune evasion, e.g. by suppressing anti-tumor T cell responses [72]. ADCs targeting B7-H3 are under clinical evaluation, including MGC018, which incorporates a duocarmycin-based payload, and DS-7300, which delivers a topoisomerase I inhibitor [73].

Another potential cell surface target is AXL, a receptor tyrosine kinase that mediates epithelial-mesenchymal transition, resistance to targeted therapies, and immune escape. AXL-directed ADCs, such as mecbotamab-V, are being investigated in NSCLC, including for patients with acquired therapeutic resistance (clinical trial reference NCT04681131).

Integrin β6 (ITGB6) is another emerging cell surface target. ITGB6 receptor is involved in tumor invasiveness, extracellular matrix remodeling, and metastatic progression. Normal expression is upregulated in several epithelial cancers. A phase 3 clinical trial is testing Sigvotatug-V in previously-treated patients with non-squamous NSCLC, after chemotherapy and immunotherapy, who have not previously been exposed to an anti-microtubule agent. This trial highlights growing interest in ADC-immunotherapy combinations (NCT06758401) [74].

Finally, other ADC targets under investigation in NSCLC reflect the diversity of tumor biology and resistance mechanisms. They include, nectin-4, NaPi2b, ROR2, PD-L1 (i.e HLX43), PTK7, ALCAM, FRα, 5 T4, CD44 variant 9 and transferrin receptor-1 (CD71; CX2029) [75–78].

1.1.4. ADC targets for small cell lung cancer

In the last decade, growing insight into the biology of SCLC has spurred strong interest in ADC [79,80]. The main current ADC targets for SCLC are as follows:

- *B7-H3*

B7-H3, widely expressed in SCLC is associated with poor prognosis. As mentioned above, anti-B7-H3 ADCs have been developed and some are in clinical trials, including in SCLC patients: *(i)* Infinatamab-DXd (I-DXd), a humanized anti–B7-H3 IgG1 conjugated to the topoisomerase I inhibitor deruxtecan, *(ii)* HS-20093, an anti–B7-H3 ADC with a topoisomerase I inhibitor (exatecan-derivative), (*iii*) miroztamab-clezutoclax, an anti–B7-H3 antibody with a BCL-XL inhibitor and *iv*) DS-7300, using an exatecan-derived topoisomerase I inhibitor [81,82]. Overall, clinical trials showed that ADCs carrying topoisomerase I inhibitor payloads have a high level of efficacy compared to standard of care, however the progression free survival (PFS) remained modest, consistent with development of resistance. Moreover, there was no correlation between B7-H3 IHC expression and an objective response, suggesting that efficacy in SCLC may possibly be due to drug delivery issues than the biomarker threshold [71].

- *DLL3*

Delta-like protein 3 (DLL3) is an atypical inhibitory ligand of the NOTCH receptor, expressed at low levels in normal tissue but highly enriched in neuroendocrine SCLC [83,84]. One of the most advanced anti–DLL3 ADC was rovalpituzumab-tesirine (Rova-T), a humanized anti–DLL3 monoclonal antibody linked to a pyrrolobenzodiazepine (PBD) dimer toxin [85]. However, even when DLL3 expression was high, ADCs produced modest response rates, short PFS and lack of benefit in overall survival, compared with topotecan. Heterogeneity and therapy-induced DLL3 loss ultimately precluded durable benefit. In contrast, tarlatamab, a DLL3 × CD3 bispecific T-cell engager, bypasses payload delivery entirely [86].

- *SEZ6*

The transmembrane protein SEZ6 is a neuroendocrine marker, expressed in SCLC and other neuroendocrine tumors [87]. ABBV-706, an anti–SEZ6 ADC with a topoisomerase I inhibitor payload, demonstrated high activity in pre-clinical studies of SCLC, neuroendocrine neoplasms, and brain tumors [88]. Early ABBV-706 data suggest that the topoisomerase I payloads may deliver a higher initial activity greater than calicheamicin-based ABBV-011, highlighting the importance of the choice of payload for SCLC [89]. Given the relatively high objective response rate (ORR) with ABBV-706, it will be critical to establish whether SEZ6 expression thresholds, heterogeneity and/or adaptive downregulation, can determine efficacy [87].

- *Other potential ADC targets*

TROP2 ADCs can produce meaningful tumor responses in relapsed SCLC, but the PFS remains short in both platinum-sensitive and platinum-resistant subgroups [5]. CD56 (NCAM1) is low in normal tissue and overexpressed in 95% of SCLC cases [79]. Lorvotuzumab-mertansine, an anti–CD56 ADC with a microtubule inhibitor payload, was evaluated in non-treated SCLC in combination with carboplatin/etoposide *vs* carboplatin/etoposide alone [79,90]. This first-generation ADC was modified with better linkers and more potent payloads and results are expected soon. Whether a topoisomerase-based strategy can also exploit a high level of expression of CD56 remains to be determined.

2. Challenges and constraints for thoracic pathologists

Taken together, clinical trial data on ADCs indicates that optimal selection of patients will likely require urgent integration of genome, proteomic and histopathological data and the emergence of multiple new predictive biomarkers in thoracic pathology opens up significant challenges to routine practice [23,25]. The introduction of additional biomarkers to be evaluated in-house by IHC, competes with the current range of established predictive biomarkers that are routinely tested. Some key challenges are described in Table 2 and are discussed below.

2.1. Optimal management of tissue and cytological samples

Tissue biopsies are commonly small in size and contain variable numbers of tumor cells. The ability to extend the range of biomarkers that can predict a therapeutic response is directly linked to the quantity and quality of the tumor tissue available in the biopsy.

The emergence of ADCs further complicates tissue biopsy management. The addition of multiple and mandatory predictive biomarkers, some of which can only be identified using IHC, requires preparation of supplementary tissue sections. Thus, new algorithms for biomarker testing in thoracic oncology are needed. The concept of “ultra personalized medicine” in thoracic oncology demands “ultra personalized” thoracic pathology. Obtaining the whole spectrum of predictive biomarkers will be the pathologist’s responsibility, so algorithms must be established together with pathologists and physicians, to define priorities according to the specimen and the patient/clinical context. The thoracic pathologist must: *i*) make an accurate and rapid histological diagnosis, including TTF1 and/or P40 and/or neuroendocrine IHC, and PD-L1 IHC assessment, *ii*) perform molecular testing for a targeted therapy strategy, using testing for single gene(s) (SGT) and/or next generation sequencing (NGS) and *iii*) now look for ADC targets using IHC and molecular testing. The transfer of predictive biomarkers for ADCs from tissue biopsies to cytological samples is a challenge, hence characterization of

Table 2
Challenges and recommendations associated with the implementation of immunohistochemistry associated with the arrival of antibody-drug conjugates in thoracic pathology. IVDR: In Vitro Diagnostics Regulation; ROSE: Rapid On Site Evaluation; TAT: Turn Around Time; GDPR: General Data Protection Regulation; EQA: External Quality Assessment.

ADC biomarker testing using IHC – Challenges and recommendations

Parameters	Challenges	Recommendations
1. Samples	• **Tissue biopsy** o Limited number and size o Variable percentage of tumor cells o Presence of necrosis • **Cytological specimens** o Quality variability on smears o Limited cellularity on cytoblocks o Insufficient number of tumor cells • **Heterogeneity** o Intra-tumoral heterogeneity o Inter-tumoral heterogeneity	• Increase biopsy number when feasible • Potential development of cryobiopsy technology • Place one tissue biopsy only in each cassette • Adapt sampling strategy according to tumor site accessibility • Establish an optimal oncologist-pathologist dialogue • Implement the ROSE procedure • Favor cytoblocks over smears for molecular analysis • Integrate liquid biopsies into the diagnostic workflow
2. Pre-analytical Step	• Cold ischemia time variability • Inconsistent formalin fixative duration • Variable fixative types for cytology • Inconsistent conditions for specimen archives • Non-compliance with ISO 15189 and CAP recommendations	• Use formalin fixative exclusively • Store FFPE blocks at ≤ 22°C (ideally at 4°C), protected from light with a controlled humidity level • Store unstained slides at 4°C • Ensure strict compliance with ISO15189 and CAP recommendations
3. Analytical Step	• Different antibody clones available for the same target • Multiple biomarker targets to master at the same time • Different scoring systems/cutoffs for the same target • Risk of tissue specimen exhaustion • Variability between IHC instruments • Variability between digital scanners • Inter-pathologist variability in assessment • Multiple AI algorithms and computational pathology tools available	• Use CE-IVD certified clones only • Conduct comparative studies o Inter-instrument for IHC o Inter-slide scanners o Inter-CE-IVD clones • Implement multiplex IHC when appropriate • Consider RNA expression analysis • Validate AI tools and computational pathology studies • Apply FDA-approved clones, scores and cutoffs
4. Post-analytical Step	• TAT for comprehensive biomarker reporting • Multiple EQAs schemes • Multiple accreditation requirements • IVDR constraints	• Establish optimal dialogue between clinical and molecular pathologists • Implement efficient IT systems • Develop inter-laboratory validation networks • Create national recommendations and support for set up IVDR procedures
5. Request Strategy	• Absence of universal international guidelines • Multiple clinical trials with uncertain outcomes	• Follow international recommendations (ESMO, NCCN, CAP, ECP) • Prioritize FDA-approved biomarkers • Establish institutional testing algorithms
6. Economic Plan	• Costs for reagents, EQAs, and data storage • Personnel costs and training expenses • Equity access to testing	• Negotiate national agreements for reimbursement • Implement AI support to optimize workflow • Establish public–private partnerships for funding • Establish public–private partnerships for funding • Rationalize testing strategies
7. Outsourcing *versus* On-site Testing	• TAT considerations • Access (or lack of access) to raw data • Workload management • Ethical rules and GDPR constraints	**Favor decentralization (on-site) if:** **Favor centralization (outsourcing) if:** • Sufficient samples volume • Strong oncologist demand • Multidisciplinary expert team available on site • Low samples volume • Workload pressure for local laboratory • Limited or no local expertise

protein expression by IHC in cytological material requires comparative studies with IHC results obtained from matched and concurrent tissue biopsies [91]. Intra- and inter-laboratory validation and comparison of results is mandatory [36] and obtaining tissue and cytological material at the same time, from the same tumor site is another source of variability. These comparative studies would ideally be performed using cytoblocks, since cytological smears are problematic and only mastered in expert cytology laboratories [92],due to different pre-analytical steps being used for cytological smears compared to those for tissue biopsies. International IHC guidelines are required for the use of biomarkers associated with ADCs, since cytological samples from NSCLC patients are more frequently sent to pathology laboratories.

2.2. Different scores and cut-off values

According to the ADC, different IHC scores may be used to assess expression of a single protein at the tumor cell surface. For example, several ADCs have been developed to target c-MET expression in late-stage NSCLC. The cut-off to define a high level of c-MET expression varies for the specific ADC and may correspond to more than 50% or more than 90% of tumor cells showing a strong level of staining (3+). In addition, other studies have considered an H-score (staining intensity plus the percentage of cells) for c-MET IHC [93]. In practice, multiple scoring systems for a single biomarker would complicate reporting and may

generate confusion among thoracic oncologists. Moreover, variability in scoring complicates intra- and inter-laboratory validation and application of external quality assurance (EQA).

The IHC score used for HER2 overexpression in NSCLC is currently the same as for gastric carcinomas, ranging from 0 to 3+ (with IHC 0–1 + defined as HER2 negative, IHC 2+ as weak to moderate and IHC 3 + as strong when staining is observed in 10% of tumor cells) [94,95]. Note that different HER2 IHC scores apply to other solid tumors, such as breast, colon and endometrial. Hence, it can be seen that (*i*) using the same HER2 score for NSCLC and gastric cancer, may complicate interpretation and, (*ii*) the existence of multiple tumor-specific scoring systems increases the risk of misunderstanding by pathologists and oncologists.

2.3. Antibodies, pre-analytical and analytical parameters

Various antibody clones targeting the same protein recognised by an ADC are commercially available [96,97]. These clones can vary in sensitivity and specificity. Thus, depending which clones are used in ADCs, heterogeneous results in the same tumor sample may be expected. Some clones, such as HER2 clones are approved for research-use only, while others, e.g. SP44 c-MET clone, are EU-compliant for *in vitro* diagnostic tests (CE-IVD) or are FDA-approved. Antibodies used for predictive biomarker testing, such as anti-PD-L1 and ALK clones, only CE-IVD and FDA-approved clones may be used in routine clinical practice. Certain clones used as ADC CDx can be run on some, but not all, automated IHC instruments in the USA, limiting widespread use of the CDx across countries and institutions, due to limited access to particular IHC platforms. Outsourcing samples for IHC test centralization may be a solution. In the past, other predictive biomarkers of lung cancer have been validated across IHC instruments [98,99],now the same is required for individual CE-IVD clones for biomarker-ADC. In addition, pre-analytical phase process steps must be mastered: to mention the main parameters, epitopes may be more- or less-sensitive to cold ischemia, formalin fixative or collection time [100]. Lastly, the importance of quality control (QC) and EQA processes in on-site clinical testing in this developing area cannot be overstated. [101,102] Given the increasing number of proteins to be rapidly assessed for expression, the QC/EQA requirements will be challenging for many laboratories, due to increasing costs and workload. A global trend toward workforce reduction in pathology laboratories means increasing the number of IHC, participating in QC/EQA and ensuring the proper turnaround times for therapeutic decision-making will increase workflow pressure in pathology laboratories, so outsourcing to central laboratories or commercially available platforms, may be necessary.

2.4. Recommendations and perspectives

International consensus is urgently needed to define rational algorithms for use of biomarkers associated to ADCs in daily practice. As structural and logistical difficulties in pathology described above may hinder worldwide access to biomarker-associated ADCs, some practical and novel technological solutions and perspectives on the use of computational and artificial intelligence (AI) are offered below: (Table 2 and Fig. 1).

2.5. Management and control of tissue biopsies

The increased number of targeted therapies, immunotherapies and ADCs for lung cancer requires concomitant genomic and IHC testing. The challenge lies in being able to screen for all therapeutic targets, using a single biopsy, while accounting for the depletion of tumor tissue resulting from sequential multiple tests. The size of bronchial biopsies varies depending on the tumor's location within the lung parenchyma and its accessibility using bronchoscopic instruments, which come in various calibers. Certain technologies, such as those involving cryobiopsy, help optimize the availability of tissue samples. According to some studies, this allows both morphological analysis and optimization of the IHC and molecular results [103–106]. However, these approaches are more expensive than techniques using forceps technologies and may be associated with more side effects, like bleeding and pneumothorax [106]. Multiple bronchial or transthoracic biopsies, taken at one biopsy per cassette, allows selection of specimens for the additional techniques, including IHC and molecular assays, particularly NGS [107]. Additional tissue-sparing can be achieved via protocols for dissecting small samples, thereby avoiding specimen exhaustion.

2.6. Multiplex immunofluorescence (QIF), chromogenic immunohistochemistry and proteomics

Sequential single-marker IHC is a multiplex staining technique where different antibodies are applied to a tissue section, one after another, with elution or "stripping" between antibody applications. This technique is becoming increasingly feasible (as an alternative to conventional IHC, which uses multiple tissue sections) and has been widely validated in pathology for immunofluorescence, (including quantitative) and chromogenic markers [102,108–113]. In future proteomics tools, such as multiplexed selected reaction monitoring mass spectrometry (SRM MS) may also be applied [112]. The question is how to quickly bridge the gap between these innovative tools and their implementation in everyday practice. Urgent solutions are required to overcome current constraints, in particular: the high cost of in-house multiplex assays; setting scoring and cut-off values for different staining intensity (considering validation mandated by clinical trials); data analysis; reporting turnaround time; CE-IVD or FDA regulatory approval; and complexity of QC/EQA programs.

Artificial intelligence (AI) algorithms may be able to solve some of these bottlenecks [114,115] (see below).

2.7. RNA-based analysis

Spatial transcriptomics allows multiple RNA expression mapping in formalin-fixed, paraffin-embedded tissue sections. Its use in pathology is nascent, and its use for biomarker detection will need validation in clinical trials of ADCs. However, it may represent a tissue-sparing method of simultaneous gene expression evaluation of several ADC targets [116]. A limitation of this technique is obtaining sufficient quality RNA from the tumor, the current requirement being a limit of greater than 50% of tumor cells in the specimen for effective performance. This level is not found in many thoracic tissue biopsies. Comparative results for protein expression obtained for the same set of molecular targets would be required. In addition, the cost of reagents and instruments as well as expertise need to be considered.

2.8. Artificial intelligence (AI) and computational pathology

Digital pathology is developing worldwide and proving to be a valuable diagnostic aid, particularly in image analysis [117] that combined with AI has led to the concept of computational pathology [114]. Quantitative continuous scoring (QCS) is an example, with objective and improved precision, sensitivity and specificity of immunostaining of protein biomarkers in tissue slides, assisting targeted drug use [118]. QCS can be used to measure the distance between stained cells and the ratio between tumor cell membrane and intra-cytoplasmic staining integrated with (NMR QCS) [119,120] the optical density of the staining and the percentage of stained tumor cells [119].

An example of NMR QCS is its use for TROP2 IHC in clinical trials [119]. Traditional IHC for TROP2 was not successful in predicting TROP2 ADC for lung cancer, whereas the NMR QCS TROP2 identified good responders to anti-TROP2 treatment at or below the usual cutoff

ratio. However, the promise of this approach is tempered by technological limitations: (i) Currently only one TROP2 clone is approved (EPR20043, Roche Ventana, Tucson, AZ USA), which means that staining can only be performed on a Ventana Benchmark instrument. (ii) Stained slides must be scanned on specific Roche Diagnostics scanners [119]. (iii) The AI algorithms used to determine the grading threshold are also unique and were originally developed by Definiens (Utrecht, Netherlands) and Roche Diagnostics (Tucson, AZ, USA). This example shows it is possible to develop an FDA approved CDx, in which a specific clone, a staining platform, a scanner and an AI tool, are integrated to ensure a high level of reproducibility [121]. In the future, the use of this assay could be limited to a selection of pathology laboratories that have the requisite equipment. Slides or formalin-fixed paraffin blocks (FFPE) could be sent to a central laboratory for full or partial processing.

Alternatively, testing could be developed in-house. To validate the current process and reproduce the same clinical results using other clones and/or staining instruments, scanners and AI tools, poses a significant challenge (Fig. 2) but if successful, could allow inter-laboratory validation of in-house NMR TROP2 QCS testing. In addition to constraints around NMR QCS, pre-analytical parameters must also be standardized. These include cold ischemia time, duration of formalin fixation (according to sample size), age of FFPE blocks, tissue section thickness, unstained slide stability, type of cover slip, mounting medium, and specimen storage temperature. Finally, cytological samples such as cytoblocks could be used for NMR QCS. However, they would need to be validated against matched tissue biopsy specimens.

In future, other algorithms based on AI will be useful to evaluate the various protein targets of ADCs [115]. The European Society for Medical Oncology (ESMO) recently released recommendations on AI-based biomarker use in oncology [122]. In addition to QCS tools, another emerging method to quantify expression of proteins targeted by ADCs (TROP2, HER2, HER3, EGFR) is quantitative immunofluorescence (QIF) [123].

2.9. Detection of biomarkers for ADCs in liquid biopsies

Liquid biopsies could potentially serve as a source of predictive protein biomarkers for ADCs in lung cancer. In addition to regular liquid biopsies (pleural effusion, fine needle aspiration (FNA) supernatants, and cerebrospinal fluid (CSF)) it may also be possible to detect expression in circulating tumor cells (CTC) isolated from blood samples [124]. However, despite promising advances over many years, difficulties are associated with the multitude of CTC detection methods, the variable reproducibility of results as well as the sensitivity and specificity of the tests, and finally, the cost and time required to obtain results [125,126]. Establishing a reliable cut-off and scoring parameters is dependent on the number of isolated CTCs, and is therefore complex. In lung cancers, CTC-based tests may be feasible for SCLC, where CTCs are abundant. However, the paucity of CTCs in NSCLC will likely limit its application in those patients [124,125].

Finally, it may be worthwhile in the future to develop a QCS for immunostained CTCs. The level of protein expression measured in plasma samples by enzyme-linked immunosorbent assay (ELISA) offers the possibility of quantifying different protein targets for ADCs.

3. Optimisation of clinical and molecular pathology

Recent results show that some ADCs are more effective in the presence of associated targetable genomic alterations, particularly *EGFR* mutations [3,127]. This paves the way for combining targeted therapies and ADCs, either simultaneously or sequentially. For this to occur, results from both IHC and molecular testing must be available at the same time to enable therapeutic decision-making. The concept of 'integrative pathology', aimed at managing the workflow of samples and analyses, is therefore essential. Not all pathology laboratories are capable of integrating the analyses into a single step, hence the need to outsource testing of samples for coordinated IHC and molecular tests to expert centers.

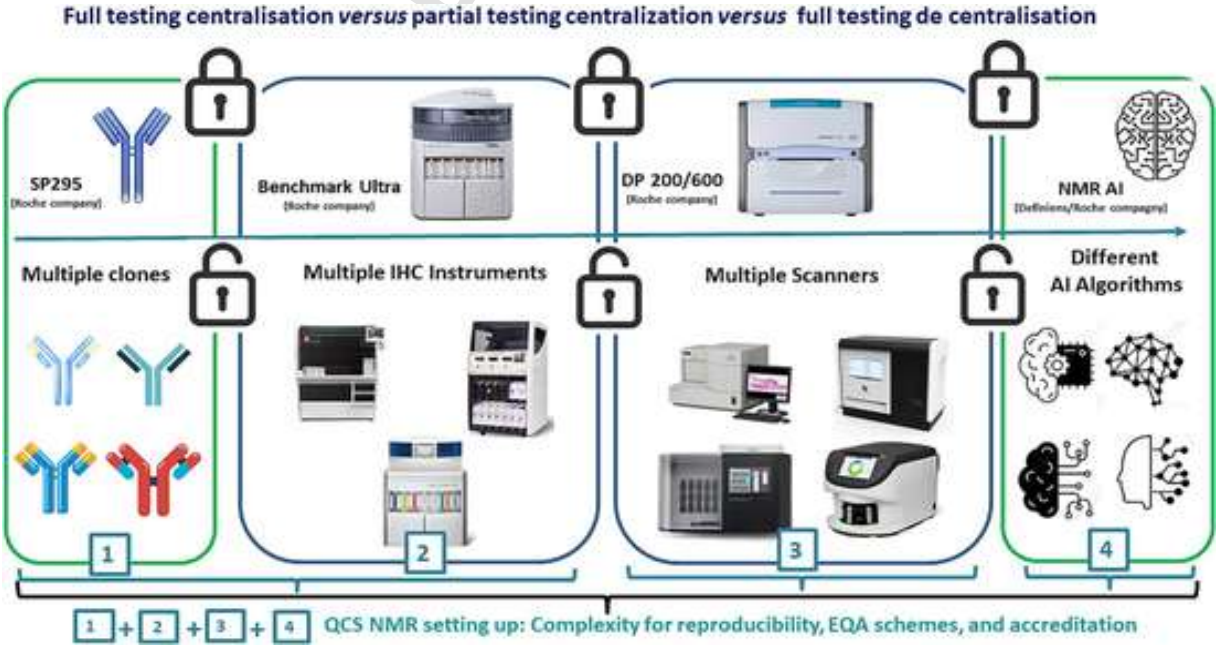

Fig. 2. Strategies and drawbacks for setting up quantitative continuous scoring (QCS) in thoracic pathology.

4. Conclusion

ADCs are rapidly emerging as treatments for patients with NSCLC and SCLC, and have proven effective across diverse histological and molecular subtypes. This new therapeutic strategy and the variety of ADCs, present biochemical and clinical challenges for pathologists in their daily practice (Fig. 3), with some of them requiring analysis of protein expression and genomic alterations, tests that must be validated in-house before being used in routine clinical pathology practice. Alternatively, testing might be outsourced to specialized laboratories. To date, predictive biomarkers have only been tested in clinical trials and promising tools such as NMR QCS are still under development. The various constraints described herein must be taken into account and addressed in order to identify the best analytical approaches for optimizing therapeutic algorithms. In addition, these advances and the resulting tools in the future must be accessible to all cancer patients, to ensure equitable access to lung cancer care.

New developments and assays can be costly and may not be reimbursed, depending on the countries and institutions [128]. Increased understanding of the pathophysiology of lung cancer, development of ADCs and emerging technical tools are likely to improve stratified treatment, guided by the results of robust CDx. It is worth noting, however, that recent clinical trials have shown that not all ADCs require a CDx test [20], thus calling into question the need to choose between a personalized treatment strategy or a universal treatment strategy.

AI tools are expected to improve selection of multiple biomarkers associated with ADCs, but harmonized international guidelines and standards are needed [122,129], particularly as future treatments may involve combinations of therapies, each requiring a specific predictive biomarker. Progress could be made through the widespread use of NMR QCS testing, as this tool has already demonstrated its ability to enhance *in situ* signals to better identify predictive biomarkers.

CRediT authorship contribution statement

Véronique Hofman: Conceptualization, Methodology, Resources, Supervision, Writing – original draft, Writing – review & editing. **Guylène Rignol:** Conceptualization, Methodology, Resources, Supervision, Writing – original draft. **Baharia Mograbi:** Writing – original draft, Writing – review & editing. **Marius Ilié:** Conceptualization, Writing – review & editing. **Mariona Riudavets:** Writing – review & editing. **Fernando Lopez-Rios:** Writing – review & editing. **Nicola Fusco:** Writing – review & editing. **Umberto Malapelle:** Writing – review & editing. **Sanjay Popat:** Writing – review & editing. **Albrecht Stenzinger:** Writing – review & editing. **David Planchard:** Writing – review & editing, Resources. **Antonio Passaro:** Writing – review & editing. **Simon Heeke:** Writing – review & editing. **Solange Peters:** Resources, Writing – review & editing. **Ignacio Ivan Wistuba:** Writing – review & editing. **Fred R. Hirsch:** Resources, Writing – review & editing. **Paul Hofman:** Conceptualization, Methodology, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

Funding

This research received no specific funding from any funding agency in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **VH** (no COIs); **GR** (no COIs); **BM** (no COIs); **MI** reports honoraria for advisory board participation from Daichi Sankyo, Bristol-Myers Squibb and AstraZeneca; **MR** (no COIs); **FLR** reports receiving grants or contracts from Thermo Fisher, AstraZeneca, Janssen, Roche, Lilly and Pfizer. He has served as a consultant for Roche, AstraZeneca, AbbVie, MSD, BMS, Janssen and Daiichi Sankyo. He has received payment or honoraria for lectures, presentations, or speakers' bureau from Roche,

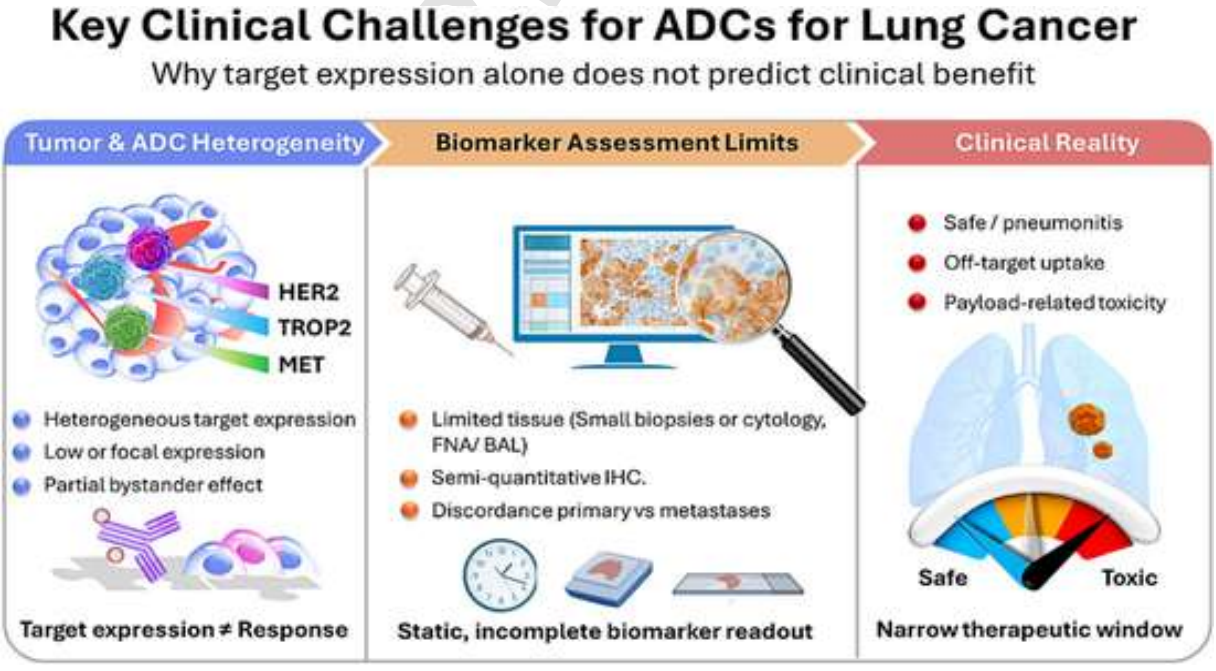

Fig. 3. Challenges and current limitations when using an antibody-drug conjugate in thoracic oncology. FNA: fine needle aspiration; BAL: broncho-alveolar lavage; IHC: immunohistochemistry.

Pfizer, Lilly, Thermo Fisher, AstraZeneca, Bayer, Merck, MSD, Novartis, Janssen, Daiichi Sankyo, Regeneron and Boehringer Ingelheim. He has received support for attending meetings or travels from MSD, Roche and Astra- Zeneca. **NF** reports consulting/advisory role: Abbvie, Alira Health, AstraZeneca, Epredia, Gilead, Menarini Group, Merck, MSD, Novartis, Owkin, Pfizer, Roche, Sakura, Signatur Bio, Sysmex, Veracyte. Speaker bureau: AstraZeneca, Daiichi Sankyo, Epredia, Exact Sciences, Gilead, GSK, Leica Biosystems, Lilly, Menarini Group, MSD, Novartis, Roche, Sysmex, ThermoFisher, Veracyte. Research support: AstraZeneca, Gilead, GSK, Menarini, Novartis, Owkin, Pfizer, Pillar Biosciences, Roche. Travel support: AstraZeneca, Novartis, Roche; **UM** reports personal fees (as consultant and/or speaker bureau) from Amgen, Boehringer Ingelheim, Diaceutics, Eli Lilly, GSK, Merck, MSD, Roche, Thermo Fisher Scientific; and from AstraZeneca, Diatech, Hedera, Janssen, Novartis unrelated to the current work; **SP** reports honoraria/consultancy from: Amgen, Anheart, Arcus Biosciences, AstraZeneca, Bayer, Bicycle Therapeutics, Biontech, BMS, Boehringer Ingelheim, Daiichi Sankyo, Ellipses, Erasca, Genmab, Gilead, GlaxoSmithKline, Guardant Health, Janssen/J&J, Lilly, Merck KGaA, MSD, Nuvalent, Pfizer, PharmaMar, Pierre Fabre, Roche, Servier, Summit, Takeda, Taiho; **AS** Receipt of honoraria or consultation fees: Aignostics, Amgen, Astellas, AstraZeneca, Bayer, Beigene, Bristol Myers Squibb, Eli Lilly and Company, Illumina, Incyte, Janssen, Jazz Pharmaceuticals, Johnson&Johnon, LeoPharma, Merck Sharp & Dohme, Novartis, Pfizer, Qlucore, QuiP, Sanofi, Servier, Taiho, Takeda, Thermo Fisher Scientific Grants: Incyte, Bristol Myers Squibb, Merck Sharp &Dome, Bayer; **DP** reports consulting, advisory role or lectures: AstraZeneca, Abbvie, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Merck, Novartis, Janssen, Pfizer, Roche, Pierre-fabre, Takeda, ArriVent, Mirati, Seagen, GSK. Clinical trials research as principal or co-investigator (Institutional financial interests): AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Pfizer, Roche, Medimmun, Sanofi-Aventis, Taiho Pharma, Novocure, Daiichi Sankyo, Abbvie, Janssen, Pierre-fabre, Takeda, ArriVent, Mirati, Seagen. Travel, Accommodations, Expenses: AstraZeneca, Roche, Novartis, Pfizer, Pierre Fabre; AP reports having received honoraria for consultation/advisory roles from AstraZeneca, AbbVie, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, Janssen, Johnson & Johnson, Gilead, GSK, Merck Sharp & Dohme, Novartis, Pfizer, Roche/Genentech, MundiPharma, Summit Therapeutics, Cullinan Oncology, and Arrivent. AP has also received honoraria for lectures or participation in company-organized educational events from AstraZeneca, AbbVie, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, eCancer, Medscape, Takeda, Janssen, Johnson & Johnson, Merck Sharp & Dohme, PeerVoice, PeerView, and TouchOncology. AP is an investigator in clinical trials with institutional financial support from AstraZeneca, Boehringer Ingelheim, Janssen, Johnson & Johnson, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Merck Serono, Mirati, Pfizer, Roche/Genentech, MRC, Daiichi Sankyo, Arrivent, Summit Therapeutics, and Cullinan Oncology; SH reports consulting/speaker fees Guardant; Thermo Fisher, Olink, Roche Diagnostics, Travel support from Sophia Genetics and Research from Thermo Fisher and BMS; **SoP** reports consultation / advisory role for AbbVie, Amgen, Arcus, AstraZeneca, Bayer, Beigene, BioNTech, BerGenBio, Bicycle Therapeutics, Biocartis, BioInvent, Blueprint Medicines, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Debiopharm, Eli Lilly, F-Star, Foundation Medicine, Genmab, Genzyme, Gilead, GSK, Hutchmed, Illumina, Incyte, Ipsen, iTeos, Janssen, Qlucore, Merck Sharp and Dohme, Merck Serono, Nuvation Bio, Nuvalent, Nykode Therapeutics, Novartis, Novocure, Pharma Mar, Promontory Therapeutics, Pfizer, Regeneron, Roche/Genentech, Sanofi, Takeda, Zymeworks. Talk in a company's organized public event: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Foundation Medicine, GSK, Illumina, Ipsen, Merck Sharp and Dohme, Novartis, Pfizer, Roche/Genentech, Sanofi, Takeda; receipt of grants/research supports: Principal investigator in trials (institutional financial support for clinical trials) sponsored by Amgen, Arcus, AstraZeneca, Beigene, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, GSK, iTeos, Merck Sharp and Dohme, Mirati, Pharma Mar, Pfizer, Promontory Therapeutics, Roche/Genentech. **II W** participates in advisory boards (compensated) Genentech/Roche, Astra Zeneca, Merck, Daiichi Sankyo, Amgen, Abbvie, and Boehringer-Ingelheim, and receives research support from Genentech, Merck, Bristol-Myers Squibb, EMD Serono, Pfizer, Takeda, Amgen, Karus, Johnson & Johnson, Bayer, Iovance, 4D, and Novartis; **FRH** Participated in advisory boards (compensated); AstraZeneca/Daiichi, BMS, Regeneron, Amgen, Novocure, Oncohost, Natera, Leica, Agilent/DAKO. Patent (through University of Colorado):"EGFR protein and gene copy number as predictive biomarkers for EGFR-directed therapies" Board of Directors: Chosa Oncology AB Consultancy: Henlius/Fosun. Regeneron; **PH** reports consulting fees and honoraria for advisory board participation from ThermoFisher Scientist, Illumina, Qiagen, Amgen, Bristol-Myers Squibb, Biocartis, Novartis, Roche, GSK, MSD, Pierre Fabre, Bayer, Biodena, Sophia Genetics, Daichi Sankyo, Pfizer, Eli Lilly, and AstraZeneca.

Acknowledgements

This work was supported by the French National Research Agency (IHU RespirERA France 2030 program # ANR-23-IAHU-0007), the FHU OncoAge and the COALA network (Cure Oncogene-Addicted Lung Adenocarcinoma), LABREXCMP24-001 – Inca_18791. F.L.R. is supported by the Tom Crean Expedition.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2026.109507.

References

[1] N. Frost, M. Reck, Non–small cell lung cancer metastatic without oncogenic alterations, Am. Soc. Clin. Oncol. Educ. Book 44 (2024) e432524.
[2] L.E.L. Hendriks, et al., Non-small-cell lung cancer, Nat. Rev. Dis. Primer 10 (2024) 71.
[3] M.-L. Meyer, et al., New promises and challenges in the treatment of advanced non-small-cell lung cancer, Lancet 404 (2024) 803–822.
[4] M. Liu, et al., Quantitative measurement of HER2 expression in non–small cell lung cancer with a high-sensitivity assay, Mod. Pathol. 37 (2024) 100556.
[5] P.-L. Su, et al., Recent advances in therapeutic strategies for non-small cell lung cancer, J. Hematol. Oncol. 18 (2025) 35.
[6] S.J. Adams, et al., Lung cancer screening, Lancet 401 (2023) 390–408.
[7] S. Puri, et al., Therapy for stage IV non–small cell lung cancer with driver alterations: ASCO living guideline, 2026.3.0, J. Clin. Oncol. 44 (2026).
[8] J.E. Reuss, et al., Therapy for stage IV non–small cell lung cancer without driver alterations: ASCO living guideline, 2026.3.0, J. Clin. Oncol. 44 (2026).
[9] R. Colombo, J.R. Rich, The therapeutic window of antibody drug conjugates: a dogma in need of revision, Cancer Cell 40 (2022) 1255–1263.
[10] R. Colombo, P. Tarantino, J.R. Rich, P.M. LoRusso, E.G.E. De Vries, The journey of antibody–drug conjugates: lessons learned from 40 years of development, Cancer Discov. 14 (2024) 2089–2108.
[11] C. Dumontet, J.M. Reichert, P.D. Senter, J.M. Lambert, A. Beck, Antibody–drug conjugates come of age in oncology, Nat. Rev. Drug Discov. 22 (2023) 641–661.
[12] J. Fuentes-Antrás, S. Genta, A. Vijenthira, L.L. Siu, Antibody–drug conjugates: in search of partners of choice, Trends Cancer 9 (2023) 339–354.
[13] K. Liu, et al., A review of the clinical efficacy of FDA-approved antibody–drug conjugates in human cancers, Mol. Cancer 23 (2024) 62.
[14] A. Passaro, P.A. Jänne, S. Peters, Antibody-drug conjugates in lung cancer: recent advances and implementing strategies, J. Clin. Oncol. 41 (2023) 3747–3761.
[15] S. Peters, et al., Antibody–drug conjugates in lung and breast cancer: current evidence and future directions—a position statement from the ETOP IBCSG Partners Foundation, Ann. Oncol. 35 (2024) 607–629.
[16] M. Riudavets, D. Planchard, The era of antibody drug conjugates in lung cancer: trick or threat? Cancer Res. Treat. 57 (2025) 293–311.
[17] I. Salifu, et al., Antibody-drug conjugates, immune-checkpoint inhibitors, and their combination in advanced non-small cell lung cancer, Cancer Treat. Res. Commun. 36 (2023) 100713.
[18] Q. Wei, et al., The promise and challenges of combination therapies with antibody-drug conjugates in solid tumors, J. Hematol. Oncol. 17 (2024) 1.
[19] J. Zhao, et al., Navigating the landscape of EGFR TKI resistance in EGFR-mutant

NSCLC — mechanisms and evolving treatment approaches, Nat. Rev. Clin. Oncol. 23 (2026) 63–83.
[20] F.R. Hirsch, Antibody–drug conjugates in non–small cell lung cancer: where are the target and the biomarker? Clin. Cancer Res. 31 (2025) 2550–2551.
[21] J. Katrini, et al., Biomarkers for antibody–drug conjugates in solid tumors, Mol. Cancer Ther. 23 (2024) 436–446.
[22] M. Kesireddy, S.R. Kothapalli, S.G. Gundepalli, S. Asif, A review of the current FDA-approved antibody-drug conjugates: landmark clinical trials and indications, Pharm. Med. 38 (2024) 39–54.
[23] P. Hofman, et al., Current challenges and practical aspects of molecular pathology for non-small cell lung cancers, Virchows Arch. 484 (2024) 233–246.
[24] P. Hofman, S. Heeke, What makes a « good » companion diagnostic in thoracic oncology? Expert Rev. Mol. Diagn. 25 (2025) 409–412.
[25] P. Hofman, et al., Proposal of real-world solutions for the implementation of predictive biomarker testing in patients with operable non-small cell lung cancer, Lung Cancer 201 (2025) 108107.
[26] K.M. Kerr, et al., Optimizing tissue stewardship in non-small cell lung cancer to support molecular characterization and treatment selection: statement from a working group of thoracic pathologists, Histopathology 84 (2024) 429–439.
[27] M. Makarem, P.A. Jänne, Top advances of the year: targeted therapy for lung cancer, Cancer 130 (2024) 3239–3250.
[28] K. Tsuchikama, Y. Anami, S.Y.Y. Ha, C.M. Yamazaki, Exploring the next generation of antibody–drug conjugates, Nat. Rev. Clin. Oncol. 21 (2024) 203–223.
[29] A. Zippelius, S.M. Tolaney, P. Tarantino, J.P. Balthasar, G.M. Thurber, Unveiling the molecular and immunological drivers of antibody–drug conjugates in cancer treatment, Nat. Rev. Cancer 25 (2025) 925–944.
[30] R. Wang, et al., Antibody–drug conjugates (ADCs): current and future biopharmaceuticals, J. Hematol. Oncol. 18 (2025) 51.
[31] S. Li, et al., Resistance to antibody–drug conjugates: a review, Acta Pharm. Sin. B 15 (2025) 737–756.
[32] M.B. Nilsson, *et al.* Loss of Payload Sensitivity and Other Mechanisms of Resistance to T-DXd in HER2-Mutant NSCLC: Implications for Subsequent Responsiveness to HER2 TKIs. *J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer* S1556-0864(26)00007–9 (2026) doi:10.1016/j.jtho.2026.01.007.
[33] S. Crescioli, et al., Antibodies to Watch in 2025, mAbs 17 (2025) 2443538.
[34] American Society of Clinical Oncology. FDA Grants Accelerated Approval to Fam-trastuzumab Deruxtecan-nxki for HER2-mutant Non-small Cell Lung Cancer. Accessed 12 August 2022. https://www.asco.org/news-initiatives/policy-news-analysis/fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan.
[35] C. Bontoux, et al., c-Met immunohistochemistry as reflex test at diagnosis for non-small cell lung cancer: a real-world experience from a monocentric case series, J. Clin. Pathol. 78 (2023) 35–41.
[36] C. Bontoux, et al., Reproducibility of c-met immunohistochemical scoring (Clone SP44) for non–small cell lung cancer using conventional light microscopy and whole slide imaging, Am. J. Surg. Pathol. 48 (2024) 1072–1081.
[37] D.R. Camidge, et al., Telisotuzumab vedotin monotherapy in patients with previously treated c-Met protein–overexpressing advanced nonsquamous *EGFR* -wildtype non–small cell lung cancer in the phase II LUMINOSITY trial, J. Clin. Oncol. 42 (2024) 3000–3011.
[38] Y. Han, et al., Targeting MET in NSCLC: an ever-expanding territory, JTO Clin. Res. Rep. 5 (2024) 100630.
[39] L.E.L. Hendriks, J. Remon, Speeding up antibody-drug conjugate development in pretreated *EGFR* -mutant non–small-cell lung cancer, J. Clin. Oncol. 41 (2023) 5351–5355.
[40] U.S. Food and Drug Administration. FDA grants accelerated approval to telisotuzumab vedotin-tllv for NSCLC with high c-Met protein overexpression. Accessed 14 May 2025. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-telisotuzumab-vedotin-tllv-nsclc-high-c-met-protein-overexpression.
[41] D. Reinhorn, M. Moskovitz, W.D. Tap, B.T. Li, Targeting HER2 in lung cancers: Evolving treatment landscape and drug development strategies, Cancer 131 (2025) e35780.
[42] P. Trillo Aliaga, et al., HER2 in non-small cell lung cancer (NSCLC): evolution of the therapeutic landscape and emerging drugs—a long way to the top, Molecules 30 (2025) 2645.
[43] C. Bontoux, et al., Deciphering the impact of HER2 alterations on non-small-cell lung cancer: from biological mechanisms to therapeutic approaches, J. Pers. Med. 12 (2022) 1651.
[44] P.A. Jänne, et al., Final analysis results and patient-reported outcomes from DESTINY-Lung02—a dose-blinded, randomized, phase 2 study of trastuzumab deruxtecan in patients with HER2-mutant metastatic NSCLC, J. Thorac. Oncol. 20 (2025) 1814–1828.
[45] Y. Lee, B. Lee, Y.-L. Choi, D.-W. Kang, J. Han, Clinicopathologic and molecular characteristics of HER2 (ERBB2)-altered non–small cell lung cancer: implications for precision medicine, Mod. Pathol. 37 (2024) 100490.
[46] B.T. Li, et al., Ado-trastuzumab emtansine for patients with *HER2* -mutant lung cancers: results from a phase II basket trial, J. Clin. Oncol. 36 (2018) 2532–2537.
[47] B.T. Li, et al., Trastuzumab deruxtecan in *HER2* -mutant non–small-cell lung cancer, N. Engl. J. Med. 386 (2022) 241–251.
[48] F. Meric-Bernstam, et al., Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: primary results from the DESTINY-PanTumor02 phase II trial, J. Clin. Oncol. 42 (2024) 47–58.
[49] M. Riudavets, I. Sullivan, P. Abdayem, D. Planchard, Targeting HER2 in non-small-cell lung cancer (NSCLC): a glimpse of hope? An updated review on therapeutic strategies in NSCLC harbouring HER2 alterations, ESMO Open 6 (2021) 100260.
[50] E.F. Smit, et al., Trastuzumab deruxtecan in patients with metastatic non-small-cell lung cancer (DESTINY-Lung01): primary results of the HER2-overexpressing cohorts from a single-arm, phase 2 trial, Lancet Oncol. 25 (2024) 439–454.
[51] E.F. Smit, Trastuzumab deruxtecan in HER2-mutant non-small-cell lung cancer: a plain language summary of the DESTINY-Lung01 study, Future Oncol. 20 (2024) 1961–1971.
[52] D. Planchard, et al., Trastuzumab deruxtecan in patients with HER2-overexpressing NSCLC: results from part 1 of the open-label, multicenter, phase 1b DESTINY-Lung03 trial, J. Thorac. Oncol. (2025) 103541, https://doi.org/10.1016/j.jtho.2025.12.080.
[53] U.S. Food and Drug Administration. FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for HER2-mutant non-small cell lung cancer. Accessed 05 may 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-her2.
[54] P. Kuo, et al., Trop-2 expression in non–small cell lung cancer, PLoS One 20 (2025) e0321555.
[55] X. Li, J. Chen, TROP2: as a promising target in lung cancer, Front. Oncol. 15 (2025) 1569897.
[56] C. Parisi, L. Mahjoubi, A. Gazzah, F. Barlesi, TROP-2 directed antibody-drug conjugates (ADCs): the revolution of smart drug delivery in advanced non-small cell lung cancer (NSCLC), Cancer Treat. Rev. 118 (2023) 102572.
[57] B.E. Nelson, F. Meric-Bernstam, Leveraging TROP2 antibody-drug conjugates in solid tumors, Annu. Rev. Med. 75 (2024) 31–48.
[58] M.-J. Ahn, et al., Datopotamab deruxtecan versus docetaxel for previously treated advanced or metastatic non–small cell lung cancer: the randomized, open-label phase III TROPION-Lung01 study, J. Clin. Oncol. 43 (2025) 260–272.
[59] J. Sands, et al., Datopotamab deruxtecan in advanced or metastatic non–small cell lung cancer with actionable genomic alterations: results from the phase II TROPION-Lung05 study, J. Clin. Oncol. 43 (2025) 1254–1265.
[60] U.S. Food and Drug Administration. FDA grants accelerated approval to datopotamab deruxtecan-dlnk for EGFR-mutated non-small cell lung cancer. Accessed 23 June 2025. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-datopotamab-deruxtecan-dlnk-egfr-mutated-non-small-cell-lung-cancer.
[61] T. Cascone, *et al.* NeoCOAST-2: Efficacy and Safety of Neoadjuvant Durvalumab (D) + Novel Anticancer Agents + CT and Adjuvant D ± Novel Agents in Resectable NSCLC. in (2024 World Conference on Lung Cancer).
[62] W. Fang, et al., Sacituzumab tirumotecan versus docetaxel for previously treated *EGFR* -mutated advanced non-small cell lung cancer: multicentre, open label, randomised controlled trial, BMJ 389 (2025) e085680.
[63] W. Fang, et al., Sacituzumab tirumotecan in EGFR-TKI–resistant, *EGFR* -mutated advanced NSCLC, N. Engl. J. Med. 394 (2026) 13–26.
[64] Q. Chen, G. Jia, X. Zhang, W. Ma, Targeting HER3 to overcome EGFR TKI resistance in NSCLC, Front. Immunol. 14 (2024) 1332057.
[65] R.A. Soo, et al., HER3 is widely expressed across diverse subtypes of NSCLC in a retrospective analysis of archived tissue samples, Future Oncol. 20 (2024) 2961–2970.
[66] H.A. Yu, et al., Translational insights and overall survival in the U31402-A-U102 study of patritumab deruxtecan (HER3-DXd) in EGFR-mutated NSCLC, Ann. Oncol. 35 (2024) 437–447.
[67] A. Gazzah, et al., Safety, pharmacokinetics, and antitumor activity of the anti-CEACAM5-DM4 antibody–drug conjugate tusamitamab ravtansine (SAR408701) in patients with advanced solid tumors: first-in-human dose-escalation study, Ann. Oncol. 33 (2022) 416–425.
[68] A. Gazzah, et al., Biomarker analysis from a phase 1/1b study of tusamitamab ravtansine in patients with advanced non-small cell lung cancer, Transl. Oncol. 63 (2026) 102615.
[69] A.-M. Lefebvre, et al., The search for therapeutic targets in lung cancer: Preclinical and human studies of carcinoembryonic antigen-related cell adhesion molecule 5 expression and its associated molecular landscape, Lung Cancer 184 (2023) 107356.
[70] Sanofi. Sanofi announces end of program evaluating tusamitamab ravtansine after a 2L NSCLC Phase 3 trial did not meet a primary endpoint. Accessed 21 December 2023. https://www.sanofi.com/en/media-room/press-releases/2023/2023-12-21-06-30-00-2799759.
[71] B. Huang, L. Chen, B7-H3 as a universal target for solid tumor therapy: clinical promise and biological complexity, J. Clin. Oncol. 44 (2026) 335–337.
[72] U. Malapelle, et al., B7-H3/CD276 inhibitors: is there room for the treatment of metastatic non-small cell lung cancer? Int. J. Mol. Sci. 23 (2022) 16077.
[73] K. Feustel, J. Martin, G. Falchook, G.S. B7-H3 inhibitors in oncology clinical trials: a review, J. Immunother. Precis. Oncol. 7 (2024) 53–66.
[74] M. Reck, et al., Frontline sigvotatug vedotin plus pembrolizumab vs pembrolizumab for non-small cell lung cancer with PD-L1 tumor proportion score ≥50%: phase III study design, Future Oncol. 21 (2025) 3891–3901.
[75] V. Boni, et al., Praluzatamab ravtansine, a CD166-targeting antibody–drug conjugate, in patients with advanced solid tumors: an open-label phase I/II trial, Clin. Cancer Res. 28 (2022) 2020–2029.
[76] D.E. Gerber, et al., Phase Ia study of anti-NaPi2b antibody–drug conjugate lifastuzumab vedotin DNIB0600A in patients with non–small cell lung cancer and platinum-resistant ovarian cancer, Clin. Cancer Res. 26 (2020) 364–372.
[77] M.J. Khosravanian, et al., Nectin-4-directed antibody-drug conjugates (ADCs): Spotlight on preclinical and clinical evidence, Life Sci. 352 (2024) 122910.
[78] S. Singh, et al., Nonclinical efficacy and safety of CX-2029, an anti-CD71 probody–drug conjugate, Mol. Cancer Ther. 21 (2022) 1326–1336.

[79] Y. Meng, et al., Antibody–drug conjugates treatment of small cell lung cancer: advances in clinical research, Discov. Oncol. 15 (2024) 327.
[80] T. Sen, et al., Emerging advances in defining the molecular and therapeutic landscape of small-cell lung cancer, Nat. Rev. Clin. Oncol. 21 (2024) 610–627.
[81] D.T. Corrigan, A. Tanwar, M. Du, A.M. Martin, X. Zang, The B7-H3 (CD276) pathway: emerging biology and clinical therapeutics, Trends Pharmacol. Sci. 46 (2025) 975–988.
[82] M. Wespiser, R. Gille, M. Pérol, Clinical progress of B7-H3 targeted antibody drug conjugate ifinatamab deruxtecan for small-cell lung cancer, Expert Opin. Investig. Drugs 34 (2025) 463–471.
[83] T. Sen, et al., Pulmonary neuroendocrine neoplasms: the molecular landscape, therapeutic challenges, and diagnosis and management strategies, Lancet Oncol. 26 (2025) e13–e33.
[84] P.-L. Su, et al., DLL3-guided therapies in small-cell lung cancer: from antibody-drug conjugate to precision immunotherapy and radioimmunotherapy, Mol. Cancer 23 (2024) 97.
[85] F. Blackhall, et al., Efficacy and safety of rovalpituzumab tesirine compared with topotecan as second-line therapy in DLL3-high SCLC: results from the phase 3 TAHOE study, J. Thorac. Oncol. 16 (2021) 1547–1558.
[86] M.-J. Ahn, et al., Tarlatamab for patients with previously treated small-cell lung cancer, N. Engl. J. Med. 389 (2023) 2063–2075.
[87] E. Gezelius, et al., Seizure-related homolog protein 6 (SEZ6): biology and therapeutic target in neuroendocrine carcinomas, Clin. Cancer Res. 31 (2025) 4419–4428.
[88] S.R. Chandana, J. Noura, C. First-in-human study of ABBV-706, a seizure-related homolog protein 6 (SEZ6)–targeting antibody-drug conjugate (ADC), in patients (pts) with advanced solid tumors. - ASCO. in (Journal of, Clin. Oncol. (2024), https://doi.org/10.1200/JCO.2024.42.16_suppl.3001.
[89] D. Morgensztern, et al., A phase I first-in-human study of ABBV-011, a seizure-related homolog protein 6–targeting antibody–drug conjugate, in patients with small cell lung cancer, Clin. Cancer Res. 30 (2024) 5042–5052.
[90] K.R. Whiteman, et al., Lorvotuzumab mertansine, a CD56-targeting antibody-drug conjugate with potent antitumor activity against small cell lung cancer in human xenograft models, mAbs 6 (2014) 556–566.
[91] M. Ilie, et al., Use of the 22C3 anti–programmed death-ligand 1 antibody to determine programmed death-ligand 1 expression in cytology samples obtained from non–small cell lung cancer patients, Cancer Cytopathol. 126 (2018) 264–274.
[92] S. Suikkanen, S.M. Remes, I. Tuominen, Role of preanalytical phase and laboratory process for optimal ancillary testing in cytopathology, Acta Cytol. 70 (2025) 113–125.
[93] D.R. Camidge, et al., Phase I study of 2- or 3-week dosing of telisotuzumab vedotin, an antibody–drug conjugate targeting c-met, monotherapy in patients with advanced non–small cell lung carcinoma, Clin. Cancer Res. 27 (2021) 5781–5792.
[94] G.R.R. Ricciardi, et al., NSCLC and HER2: between lights and shadows, J. Thorac. Oncol. 9 (2014) 1750–1762.
[95] A. Yoshizawa, et al., HER2 status in lung adenocarcinoma: a comparison of immunohistochemistry, fluorescence in situ hybridization (FISH), dual-ISH, and gene mutations, Lung Cancer 85 (2014) 373–378.
[96] X. Baez-Navarro, et al., HER2-low across solid tumours: different incidences and definitions, Pathology (Phila.) 57 (2025) 403–414.
[97] G. Cursano, et al., Inter-assay variability of TROP2 immunohistochemistry in triple-negative breast cancer, Mol. Diagn. Ther. 29 (2025) 849–857.
[98] J. Adam, et al., Multicenter harmonization study for PD-L1 IHC testing in non-small-cell lung cancer, Ann. Oncol. 29 (2018) 953–958.
[99] M. Ilie, et al., Use of the 22C3 anti–PD-L1 antibody to determine PD-L1 expression in multiple automated immunohistochemistry platforms, PLoS One 12 (2017) e0183023.
[100] C. Marchiò, et al., Part I – pre-analytical phase, Pathologica 117 (2025) 5.
[101] L.O. AbdelWareth, et al., Fast track to accreditation: an implementation review of college of American pathologists and international organization for standardization 15189 accreditation, Arch. Pathol. Lab. Med. 142 (2018) 1047–1053.
[102] M. Ilié, et al., Analytical validation of automated multiplex chromogenic immunohistochemistry for diagnostic and predictive purpose in non-small cell lung cancer, Lung Cancer 166 (2022) 1–8.
[103] M. Haentschel, et al., Cryobiopsy increases the EGFR detection rate in non-small cell lung cancer, Lung Cancer 141 (2020) 56–63.
[104] F.J. Herth, et al., Safety and performance of transbronchial cryobiopsy for parenchymal lung lesions, Chest 160 (2021) 1512–1519.
[105] T. Nishida, et al., Feasibility study of cryobiopsy for practical pathological diagnosis of primary lung cancer including immunohistochemical assessment, Jpn. J. Clin. Oncol. 51 (2021) 271–278.
[106] H. Udagawa, et al., Feasibility and utility of transbronchial cryobiopsy in precision medicine for lung cancer: prospective single-arm study, Cancer Sci. 111 (2020) 2488–2498.
[107] F. Penault-Llorca, et al., Expert opinion on NSCLC small specimen biomarker testing — part 1: tissue collection and management, Virchows Arch. 481 (2022) 335–350.
[108] N. De Souza, S. Zhao, B. Bodenmiller, Multiplex protein imaging in tumour biology, Nat. Rev. Cancer 24 (2024) 171–191.
[109] P.W. Harms, et al., Multiplex immunohistochemistry and immunofluorescence: a practical update for pathologists, Mod. Pathol. 36 (2023) 100197.
[110] P. Hofman, et al., Multiplexed immunohistochemistry for molecular and immune profiling in lung cancer—just about ready for prime-time? Cancers 11 (2019) 283.
[111] M. Ilie, et al., Automated chromogenic multiplexed immunohistochemistry assay for diagnosis and predictive biomarker testing in non-small cell lung cancer, Lung Cancer 124 (2018) 90–94.
[112] N.J. McNamee, J. Liu, R.C. Poulos, A.T. Aref, R.R. Reddel, Predictive biomarkers of antibody–drug conjugate efficacy for solid tumors: current challenges and the potential role of quantitative proteomics, Clin. Cancer Res. 32 (2026) 661–673.
[113] E.R. Parra, M. Ilié, I.I. Wistuba, P. Hofman, Quantitative multiplexed imaging technologies for single-cell analysis to assess predictive markers for immunotherapy in thoracic immuno-oncology: promises and challenges, Br. J. Cancer 129 (2023) 1417–1431.
[114] A. Aggarwal, et al., Artificial intelligence in digital pathology — time for a reality check, Nat. Rev. Clin. Oncol. 22 (2025) 283–291.
[115] P. Hofman, et al., Artificial intelligence for diagnosis and predictive biomarkers in non-small cell lung cancer patients: new promises but also new hurdles for the pathologist, Lung Cancer 200 (2025) 108110.
[116] N. Ozirmak Lermi, et al., Comparison of imaging based single-cell resolution spatial transcriptomics profiling platforms using formalin-fixed paraffin-embedded tumor samples, Nat. Commun. 16 (2025) 8499.
[117] C. Eloy, et al., Digital transformation of pathology - the European Society of Pathology expert opinion paper, Virchows Arch. 487 (2025) 971–981.
[118] S. Christ, et al., EP06.05-09 computational pathology-based assessment of cMET IHC expression for patient selection in the treatment of MET overexpressing NSCLC, J. Thorac. Oncol. 18 (2023) S497.
[119] M.C. Garassino, et al., PL02.11 normalized membrane ratio of TROP2 by quantitative continuous scoring is predictive of clinical outcomes in TROPION-Lung 01, J. Thorac. Oncol. 19 (2024) S2–S3.
[120] A. Kapil, et al., HER2 quantitative continuous scoring for accurate patient selection in HER2 negative trastuzumab deruxtecan treated breast cancer, Sci. Rep. 14 (2024) 12129.
[121] F. Lopez-Rios, et al., OA09.03 real-world assessment of TROP2-NMR by quantitative continuous scoring (QCS) in non-small cell lung carcinoma (NSCLC), J. Thorac. Oncol. 20 (2025) S29–S30.
[122] M. Aldea, et al., ESMO basic requirements for AI-based biomarkers in oncology (EBAI), Ann. Oncol. 37 (2026) 414–430.
[123] I.P. Trontzas, et al., Quantitative protein expression of antibody–drug conjugate targets in EGFR mutated and wild-type non–small cell lung cancer, Clin. Cancer Res. 31 (2025) 2767–2776.
[124] A. Mishra, et al., Circulating tumor cells predict response to the DLL3-targeting bispecific antibody tarlatamab, Cancer Discov. OF1–OF20 (2026), https://doi.org/10.1158/2159-8290.CD-25-1483.
[125] V. Hofman, et al., Detection of circulating tumor cells from lung cancer patients in the era of targeted therapy: promises, drawbacks and pitfalls, Curr. Mol. Med. 14 (2014) 440–456.
[126] C.S. Dai, et al., Circulating tumor cells: Blood-based detection, molecular biology, and clinical applications, Cancer Cell 43 (2025) 1399–1422.
[127] F. Zhou, et al., The changing treatment landscape of EGFR-mutant non-small-cell lung cancer, Nat. Rev. Clin. Oncol. 22 (2025) 95–116.
[128] D. Horgan, et al., Precision oncology: a global perspective on implementation and policy development, JCO Glob. Oncol. (2025) e2400416, https://doi.org/10.1200/GO-24-00416.
[129] D. Montezuma, et al., What practicing pathologists and oncologists should know about the new computational pathology-based companion diagnostic tools, J. Pathol. (2026) path.70045, https://doi.org/10.1002/path.70045.