

Novel Biomarkers and Drug Targets in Non-Small Cell Lung Cancer

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Disclosure:	Dy has received honoraria/consulting fees from AstraZeneca, Eli Lilly, Amgen, and Mirati Therapeutics. Dy did not receive financial compensation for this piece of work.
Acknowledgements:	This article was authored by Eleanor Roberts, Beeline Science Communications Ltd, London, UK.
Support:	The publication of this article is fully funded by Sanofi.
Disclaimer:	The opinions expressed in this article belong solely to the named interviewee.
Citation:	EMJ. 2022;7[3]:52-59. DOI/10.33590/emj/10113934. https://doi.org/10.33590/emj/10113934 .



Interview Summary

Despite therapeutic advances, the prognosis of non-small cell lung cancers (NSCLC) is still very poor, especially when first diagnosed at later stages involving metastases. NSCLC classification can be aided by identifying genetic, molecular, and histological subtypes that are important biomarkers in treatment selection. The majority of targeted therapies are now first-line treatment options for eligible patients with advanced stages of NSCLC. Here they have been shown to improve overall survival (OS) and progression free survival (PFS). Such treatments include those aimed at driver mutations in NSCLC, such as the genes for *EGFR* and *ALK*, and immune checkpoint inhibitors such as those targeting programmed death protein 1 or its ligand (programmed death ligand 1 [PD-L1]). In antibody-drug conjugates (ADC), cytotoxic payloads are conjugated to monoclonal antibodies (mAb) that deliver the drug to tumour cells expressing the corresponding target antigen. While there are still no ADCs specifically approved for NSCLC by the U.S. Food and Drugs Administration (FDA), several agents have shown promise and are being investigated as therapy in NSCLC. Emerging biomarkers as targets for ADCs with potential relevance in the treatment of NSCLC include products of the genes *CEACAM5*, *TROP2*, *HER2*, and *c-MET*. Herein, this interview provides an overview of biomarkers and targeted therapies, with a discussion with Grace Dy, Roswell Park Comprehensive Cancer Center, Buffalo, New York, USA, on their potential clinical utility.

INTRODUCTION

Surgical resection is a major treatment approach in early-stage NSCLC, along with chemoradiation for locally advanced disease.¹ For patients with locally advanced or metastatic NSCLC, selection

of therapy for NSCLC depends on several factors, including disease stage, pattern of local and/or metastatic spread, patient performance status, and comorbidities, along with biomarkers such as histological, mutation profile, and protein expression markers.

To better understand how these biomarkers and drugs could be utilised in clinical practice, EMJ discussed the success of current biomarker-based therapies, unmet needs for patients with NSCLC, the use of novel biomarkers in NSCLC, and the potential role of these biomarkers as drug targets, which are being investigated in a number of clinical trials.

THE SUCCESS OF CURRENT STANDARD OF BIOMARKER-BASED CARE FOR PATIENTS WITH NON-SMALL CELL LUNG CANCERS

Progress is being made in management of late stage NSCLC due to development of targeted therapies against various biomarkers due to better knowledge of tumour biology.² Driver mutations in NSCLC include those involving different genes such as *EGFR*, *ALK*, *KRAS*, etc.² For patients with newly diagnosed stage IV, relapsed/recurrent advanced NSCLC, and those without actionable oncogenic biomarkers, choice of therapy may include the use of immune checkpoint inhibitors (as monotherapy or in combination with chemotherapy) especially where there are no driver mutations.¹ Such immune checkpoint inhibitors include pembrolizumab, nivolumab, cemiplimab, and atezolizumab, which target programmed death protein 1 or its ligand, PD-L1;^{1,3-5} and ipilimumab, which targets cytotoxic T-lymphocyte-associated protein 4, with use dependent on expression levels.

In the advanced setting, biomarker testing is routinely used at diagnosis to select options for first and subsequent lines of treatment.¹ For example, in the UK, National Institute of Health and Care Excellence (NICE) guidelines recommend the use of biomarker testing to detect *EGFR* tyrosine kinase mutations in all patients with previously untreated, locally advanced or metastatic NSCLC.⁶ Dy stated that “testing is only carried out when there’s an impact on clinical practice. For example, testing for *EGFR* mutation status in NSCLC was only applicable in the advanced setting before December 2020 in the USA because that’s the only setting where therapy was shown to be effective. However, we now test for *EGFR* mutation status in earlier stages of disease as well as in the adjuvant setting in patients who

meet criteria for adjuvant therapy with the tyrosine kinase inhibitor (TKI) osimertinib.”

In patients with later stages of NSCLC, therapy with inhibitors against these targets can improve median PFS and/or OS.¹ For instance, in people with *EGFR*-mutated tumours and previously untreated locally advanced or metastatic NSCLC, treatment with osimertinib demonstrated a very high overall response rate of 80%, and a median PFS of 18.9 months in the FLAURA study, along with superior OS compared with patients who receive a first generation *EGFR* TKI.^{7,8} In patients with treatment-naïve advanced *ALK*-positive NSCLC, the ALEX trial of alectinib showed an overall response rate of more than 80.0%, a median PFS of 34.8 months, and superior 5-year OS compared with crizotinib.⁹ For patients with *KRAS p.G12C*-mutated advanced NSCLC previously treated with standard therapies, sotorasib has shown a response rate of around 37.0%, with a median PFS of 6.8 months, and 2-year OS of 32.5% in a pooled analysis.¹⁰

With results such as these, Dy discussed how biomarker-based treatments that were initially evaluated as second-line therapies have subsequently been approved for first-line therapy.¹ A potential exception to this generalisation, she discussed, are situations where the tumour remains sensitive to immunotherapy despite harbouring actionable mutations such as in NSCLC with a *KRAS p.G12C* mutation. “For those patients,” Dy suggested, “we would still be very comfortable starting with immunotherapy-based treatment because many patients with *KRAS* mutations can derive prolonged duration of benefit from immunotherapy if there are no additional biomarker alterations to suggest inferior outcomes with immunotherapy such as co-mutation with serine/threonine kinase 11.”^{11,12}

To illustrate, pembrolizumab has been investigated in a series of studies as mono- or combination therapy for patients with metastatic NSCLC. The KEYNOTE 024 trial showed a median OS of 30.0 months with pembrolizumab alone compared with 14.2 months with chemotherapy alone in patients with *EGFR/ALK* wildtype NSCLC harbouring a PD-L1 tumour proportion score of $\geq 50\%$.⁴ Where participants were included with any PD-

L1 tumour proportion score of >1%, OS was 17.7 months in the pembrolizumab group compared with 13.0 months in the chemotherapy group.¹³ When pembrolizumab was combined with pemetrexed-platinum in non-squamous NSCLC without *EGFR/ALK* alterations, a median OS of 22.0 months versus 10.7 months with chemotherapy alone was shown,³ with a median OS of 17.1 months with pembrolizumab plus carboplatin and paclitaxel/nab-paclitaxel versus 11.6 months for placebo plus chemotherapy.¹⁴ Similar superior OS signals were seen with ipilimumab plus nivolumab-based regimens compared with chemotherapy alone.¹⁵ Such results demonstrate why immune checkpoint inhibitor-based regimens are now first-line therapy for later disease stages of NSCLC.¹

Brain metastases are common in NSCLC, occurring in up to 40% of patients.¹⁶ Dy reported that treatment choice may be influenced by the presence of such metastases, as some therapies have better central nervous system penetrance than others.¹⁷ “Many, if not all, of these agents with better brain activity have been adopted as preferred treatment in the first-line setting,” explained Dy. The classic example is osimertinib, which has better central nervous system penetrance compared with early generation TKIs and is now the preferred first-line treatment in the USA.¹⁸

NEW BIOMARKERS AND DRUG TARGETS IN NON-SMALL CELL LUNG CANCERS MANAGEMENT

According to Dy, “there remains a need for both new drug targets as well as platforms in testing for drug targets.” Four emerging biomarkers in NSCLC are *CEACAM5*, *TROP2*, *HER2*, and *c-MET*. Mutation or amplification of these genes, or overexpression of the corresponding proteins, can influence NSCLC prognosis and treatment outcomes.¹⁹⁻²²

Carcinoembryonic antigen cell adhesion molecule 5 (*CEACAM5*) is a protein involved in cell adhesion, migration, and anoikis inhibition. This latter property may facilitate tumourigenesis and metastasis and its expression in a variety of cancers has led to it being investigated as a biomarker and therapeutic target in NSCLC.¹⁹ Tumour-

associated calcium signal transducer 2 is involved in calcium transduction as well as tumour growth, invasion, and neovascularisation. Overexpression is associated with a poor clinical course in people with lung adenocarcinoma.²⁰ Mutation, amplification, and over-expression of the transmembrane glycoprotein receptor gene *HER2* is well documented in NSCLC and associated with poorer prognosis and resistance to *EGFR*-focused TKIs in some patients with NSCLC.²¹ C-mesenchymal epithelial transition factor, a tyrosine kinase receptor, is involved in cancer cell survival, proliferation, migration, invasion, and angiogenesis and is also associated with *EGFR* and *ALK* TKI resistance.²²

In the case of *CEACAM5*, while not all NSCLC-associated tumours express this marker to a high degree (as assessed, for instance, by rating immunohistochemical stain intensity and proportion of positive stained cells), such expression was found in approximately 24% of specimens in one study.²³

CEACAM5 expression on circulating tumour cells can also be monitored in the circulation.²⁴ However, explained Dy, “a caveat here is that *CEACAM5* is non-specific. Inflammatory conditions, diarrhoea, or smoking can cause it to go up. Nonetheless, it is helpful overall in monitoring trends over time especially in lung cancer patients who are non-smokers, who have elevated *CEACAM5* levels prior to therapy.” *HER2* mutations are much rarer,²¹ and for *c-MET* “it is more complicated,” reported Dy, “as exon 14 mutation, amplification, or protein overexpression may be potentially used as biomarkers depending on the therapeutic platform utilised.”²²

However, while these biomarkers are known, Dy explained how, in the clinic, “we don’t routinely test these currently because they’re not necessarily actionable in terms of standard of care therapies. With that being said, for example, when we do find acquired resistance to TKIs such as those mediated by *c-MET* overexpression, we can now triage patients into *MET*-based trials.”

THE POTENTIAL ROLE OF EMERGING BIOMARKERS AS DRUG TARGETS IN THE TREATMENT OF PATIENTS WITH NON-SMALL CELL LUNG CANCERS

There is a role for these emerging biomarkers as drug targets, according to Dy. More recently the use of ADCs associated with CEACAM5, TROP2, HER2, and c-MET expression have been investigated for NSCLC. These consist typically of a mAb, such as tusamitamab, sacituzumab, trastuzumab, or telisotuzumab, targeting the tumour-expressed antigen, conjugated to a cytotoxic drug (termed a 'payload' or 'warhead'), such as ravtansine, deruxtecan, or vedotin. Attaching the payload to the mAb in the ADC is made possible through 'linker' molecules. The goal of ADCs is to maximise tumour cell kill, while minimising systemic toxicity to healthy cells.²⁵ Examples of these are shown in [Table 1](#).

Notably, Dy explained that "many of the ADCs in development have toxicities that are better tolerated."^{25,26} However, she added the caveat that, "of course, the toxicity profile will vary among ADCs, not just because of the target but

also because of the differences in payloads that may have unique side effects that oncologists may not be familiar with initially.^{25,26} But over time, we become more vigilant in monitoring a patient's symptoms, for example with ocular toxicities associated with maytansinoid DM4."

Dy also explained how there are many ADC trials exploring combinations with immunotherapy in the first-line setting. "We don't anticipate ADCs to replace immunotherapies," she said, "but we are looking at how we complement existing treatments. For instance, do we combine ADC with immunotherapy or targeted therapy first-line? I do foresee that ADCs would have some role, but it takes a while to develop these drugs. We must first prove the therapy's value before we can routinely implement them as a standard of care. Testing for the relevant biomarkers would certainly be absorbed into practice once we show benefit of these newer therapies." Other questions she posed that need investigating included: "How do we modify the chemotherapy regimen that is combined with immunotherapy now and do we drop one of the agents to minimise myelosuppression, depending on the payload?"

Table 1: Examples of antibody-drug conjugates.²⁵⁻³⁰

Target	Antibody	Cytotoxic payload	Linker	Payload target
CEACAM5	Tusamitamab	Ravtansine (DM4)	SPDB	Mi
TROP2	Sacituzumab	Govitecan (SN38)	Acid-labile ester	Tli
	Datopotamab	Deruxtecan (DXd)	Cleavable tetrapeptide based molecule	Tli
HER2	Trastuzumab	Emtansine (DM1)	MCC thioether	Mi
	Trastuzumab	Duocarmazine	DHA	Tli
	Trastuzumab	Deruxtecan (DXd)	Non-cleavable maleimidocaproyl	Tli
c-MET	Telisotuzumab	Vedotin (MMAE)	Valine-citrulline	Mi

CEACAM5: carcinoembryonic antigen cell adhesion molecule 5; c-MET: c-mesenchymal epithelial transition factor; DHA: duocarmycin-hydroxybenzamide-azaindol; MCC: maleimidomethyl cyclohexane-1-carboxylate; Mi: microtubule inhibitor; MMAE: monomethyl auristatin E; SPDB: succinimidyl 4-(2-pyridyldithio) butyrate; Tli: topoisomerase I inhibitor; TROP2: tumour-associated calcium signal transducer 2.

One issue associated with ADC therapy, highlighted Dy, “is the efficacy of the payload itself and the linker technology that may enable bystander killing effect.” She also highlighted how the level of molecular biomarker expression may not always correspond to how well a drug works. For instance, Dy discussed how, in her experience, the ADC trastuzumab-deruxtecan can work even in patients with *HER2* mutated NSCLC despite low *HER2* expression, as has been shown in people with advanced breast cancer with low *HER2* expression.³¹ Additional prospective studies are needed to validate and confirm these observations. However, Dy stressed that, “we’re still very enthused because we have all these new ADCs coming into the clinic showing promise in clinical trials. The next phase though is how do we incorporate testing in the setting of limited tissue and biological variations such as intra-tumour heterogeneity.”

CLINICAL UNMET NEEDS FOR PATIENTS WITH NON-SMALL CELL LUNG CANCERS

“The biggest challenge in NSCLC,” discussed Dy, “is the stage at diagnosis as usually patients are diagnosed with an advanced or a metastatic stage not amenable to surgery.” This, she highlighted, necessitates lung cancer screening programmes, as these have demonstrated benefits in terms of early diagnosis and lung cancer-specific survival and mortality outcomes.³²

Other challenges involve therapy options at different stages, and the success of such lines of treatment, and how best to treat specific metastases. Dy reported that, “while we’re able to optimise first-line therapies for specific patient populations where targeted therapy or immunotherapy can be superior to chemotherapy, the vast majority of patients, even those eligible for these therapies, will inevitably experience disease progression.” This is potentially due to resistance to targeted therapy or immunotherapy, discussed Dy, who commented that for almost all patients “we have to define what the mechanism of acquired resistance is because sometimes there is a subsequent therapy to address that resistance. Inevitably though,” she continued, “at some point, the evolutionary biology of cancer resistance

outpaces our ability to understand things and develop therapies rapidly in real-time in response to these resistance mechanisms.”

Another unmet need Dy discussed was identifying better biomarkers for immunotherapy and the need to improve on immunotherapy treatment outcomes in ‘cold tumours’ (where effector immune cell activity is suppressed) or ‘immune deserts’ (where immune cells are not in the vicinity of the tumour). There is also the problem, she highlighted, that large proportions of patients have tumours that either do not have a targeted therapy option available or are unlikely to respond well to immunotherapy.

While in Dy’s centre they look for biomarker protein overexpression using immunohistochemistry, she explained how challenges arise in the early phases of drug development due to not having standardised methods for, for example, choosing a positive/negative cut-off, defining overexpression, or having specific reagents such as the antibody for protein detection with immunohistochemistry. This, she explained, makes it difficult to rapidly implement certain biomarkers into routine practice.

A further limitation, Dy discussed, is that “tissue biopsies from patients with lung cancer are limited in amount, and it might not be easy to re-biopsy to get more tissue in many situations.” She stressed how “having multiple targeted therapies available will not be useful unless we are able to test for actionable mutations properly and expediently.” With newer biomarkers, Dy explained how they are currently mostly used for academic research. “We have all these newer pathology techniques that are being developed that might actually be tissue-sparing but at this point, deciding when to do testing is still potentially problematic because even the current standard of adequate mutation profiling is still not met for many patients.”

More widely, Dy discussed the problem of general resource variance when it comes to being able to detect, analyse, and treat NSCLC. This is not only between low- versus high-income countries, but even within the same country, for example, metropolitan versus rural areas. Cost was also an issue raised in that while there may be a number of biomarkers

that could be used to analyse NSCLC, in many countries only a limited number of biomarkers are currently covered by healthcare and insurance providers. She emphasised that even though current guidelines endorse biomarker testing for newly diagnosed patients, due to deficits in local resources, many with advanced NSCLC “may not get beyond *EGFR* and *ALK* testing despite the fact that we now have multiple effective targeted therapies.”³³

ONGOING CLINICAL TRIALS OF EMERGING BIOMARKERS

There are several ongoing Phase II and III trials of therapies associated with emerging biomarkers. For instance, in the case of *CEACAM5*, the CARMEN studies are investigating the use of tusamitamab ravtansine, including in a global Phase III trial where it is being compared with docetaxel (CARMEN-LC03; NCT04154956),³⁴ and a Phase II single arm trial combining tusamitamab ravtansine with ramucirumab to examine efficacy and toxicity (CARMEN-LC04; NCT05245071).³⁵ Also underway are CARMEN-LC05 (NCT04524689), evaluating tusamitamab ravtansine either with pembrolizumab or pembrolizumab and platinum-based chemotherapy with or without pemetrexed,³⁶ and CARMEN-LC06 (NCT05245071), evaluating tusamitamab ravtansine in participants with negative or moderate *CEACAM5* expression and high circulating carcinoembryonic antigens.³⁵

For *TROP2* mutations, there are several ADCs in development, including several TROPION trials investigating datopotamab-deruxtecan,³⁷⁻⁴³ and the EVOKE trials investigating sacituzumab govitecan-hziy (NCT05089734 and NCT05186974).^{44,45} For *HER2* mutations, there

are the DESTINY trials investigating trastuzumab deruxtecan (NCT05048797).⁴⁶ Other *HER2* selective agents under investigation include tucatinib (NCT04579380),⁴⁷ or those that can dually targeted *EGFR* and *HER2*, such as BDTX189 (NCT04209465)⁴⁸ or BAY2927088 (NCT05099172).⁴⁹

With *c-MET* mutations, Dy discussed how, aside from ADCs, other antibody-based approaches include selective agents being tested in combination with, for instance, those targeting *EGFR* mutations. Amivantamab, an *EGFR/c-MET* bispecific antibody, is approved for treatment in patients with an *EGFR* exon 20 insertion mutation in the second-line setting.⁵⁰ It is also being tested in combination with chemotherapy upfront for this patient population in the PAPILLON trial (NCT04538664).⁵¹ Amivantamab is additionally being tested in combination with lazertinib as a first-line option (NCT04965090)⁵² or in combination with chemotherapy after osimertinib failure (NCT04487080)⁵³ in patients with classic *EGFR* mutation in the MARIPOSA trial.

CONCLUSION

Despite therapeutic advances, the prognosis of NSCLC is still very poor.⁵⁴ Identification of genetically and molecularly defined NSCLC subtypes has led to development of biomarkers for such and the use of targeted therapies. Many more are also in the clinical trial phase. While use of such biomarkers and therapies has led to gains in NSCLC in terms of PFS and OS, current limitations include access to the means to analyse tumours, to the tissue needed to carry out a number of analyses, and to the therapies themselves.

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