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REVIEW

PD-L1 testing for lung cancer in the UK: recognizing the challenges for implementation

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PD-L1 testing for lung cancer in the UK: recognizing the challenges for implementation

A new approach to the management of non-small-cell lung cancer (NSCLC) has recently emerged that works by manipulating the immune checkpoint controlled by programmed death receptor 1 (PD-1) and its ligand programmed death ligand 1 (PD-L1). Several drugs targeting PD-1 (pembrolizumab and nivolumab) or PD-L1 (atezolizumab, durvalumab, and avelumab) have been approved or are in the late stages of development. Inevitably, the introduction of these drugs will put pressure on healthcare systems, and there is a need to stratify patients to identify those who are most likely to benefit from such treatment. There is evidence that responsiveness to PD-1 inhibitors may be predicted by expression of PD-L1 on neoplastic cells. Hence, there is considerable interest in using PD-L1 immunohistochemical staining to guide the use of PD-1-targeted treatments in patients with NSCLC. This article reviews the current knowledge about PD-L1 testing, and identifies current research requirements. Key factors to consider include the source and timing of sample collection, pre-analytical steps (sample tracking, fixation, tissue processing, sectioning, and tissue prioritization), analytical decisions (choice of biomarker assay/kit and automated staining platform, with verification of standardized assays or validation of laboratory-devised techniques, internal and external quality assurance, and audit), and reporting and interpretation of the results. This review addresses the need for integration of PD-L1 immunohistochemistry with other tests as part of locally agreed pathways and protocols. There remain areas of uncertainty, and guidance should be updated regularly as new information becomes available.

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Introduction

Worldwide, almost 1.6 million people die from lung cancer every year.[1] Non-small-cell lung cancer (NSCLC) accounts for ~85% of all cases[2] but, until recently, options for managing this disease were limited and often ineffective. For the ~25% of patients with early-stage disease at diagnosis, surgery or radical radiotherapy is possible. However, for the majority, in whom disease is disseminated, options are typically confined to chemotherapy or palliative radiotherapy.[3]

The advent of tyrosine kinase inhibitors (TKIs) a decade ago led to significant progress in the management of NSCLC, heralding a new and elegant approach to treatment, in which patient subgroups with particular genetic abnormalities can be accurately targeted.[4] Treatment with drugs that are active against sensitizing mutations in the epidermal growth factor receptor (EGFR) (such as erlotinib, gefitinib, and afatinib) or against anaplastic lymphoma kinase (ALK) rearrangements (such as crizotinib and ceritinib) is now standard. However, because these TKIs target only those clones of neoplastic cells with a particular genetic aberration, tumours often evolve to escape their inhibitory effect, and previously hidden or new mutations eventually emerge to render the tumour resistant.[5] In a sense, these drugs are compromised by their own specificity.

A new approach to the management of NSCLC, involving immune checkpoint inhibitors, has emerged recently. These drugs do not rely on specific targeting of the tumour, but instead work by disabling the ability of the tumour to evade the immune response of the host, which would normally recognize the neoplastic population as foreign and subject it to immune destruction.[6] Several immune checkpoint inhibitors involving ligand–receptor interactions appear to be relevant in protecting tumours from immune attack. The immunology is complex, involving antigen-presenting cells, T lymphocytes of several subsets, and neoplastic cells. The profound local immune suppression present in tumours is orchestrated by cytokines and other molecules produced by neoplastic cells or expressed on their surface (Figure 1).

With regard to NSCLC, most interest has centred on the interaction between programmed death receptor 1 (PD-1) and its ligand programmed death ligand 1 (PD-L1; also known as B7 homologue 1, encoded by the gene *CD274*). PD-1 is expressed on the surfaces of immune cells, particularly activated T lymphocytes. Its normal function is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-L1 is a transmembrane protein that is expressed at low levels by various healthy cell types (e.g. immune, vascular, endothelial and epithelial cells) but at high levels by some neoplastic cells. In the context of NSCLC, the binding of PD-1 and PD-L1 protects the tumour from immune attack.[7] Inhibition of either receptor or ligand by monoclonal antibodies removes this protective effect, exposing the tumour to immune destruction.

This strategy, known as 'immune modulation' or 'immune checkpoint inhibition', has shown great promise in human studies, and several drugs have been approved or are in the late stages of development. These include both anti-PD-1 agents (e.g. pembrolizumab and nivolumab) and anti-PD-L1 agents (e.g. atezolizumab, durvalumab, and avelumab).[8] However, there remain important and unresolved questions about the prediction of which patients are most likely to benefit from such drugs.[9] In some cancer types, such as Hodgkin lymphoma, most tumours appear to express PD-L1, and hence there may be no need to stratify patients according to expression. In other cancers, such as melanoma, PD-1 blockade is effective regardless of PD-L1 status, and again there appears to be no need to evaluate PD-L1 expression. However, for a third group of cancers, including NSCLC, there is evidence that responsiveness to PD-1 inhibitors, such as pembrolizumab and nivolumab, may be predicted by expression of PD-L1 on neoplastic cells. The role of non-neoplastic cellular expression of PD-L1, particularly on tumour-infiltrating lymphocytes (TILs), is still being studied and is a matter of much debate.

As these targeted agents become available for widespread clinical use amidst the constraints of restricted healthcare budgets and the need to optimize resource allocation, PD-L1 testing could become enormously important in NSCLC management. To ensure that treatment decisions based on PD-L1 expression are consistent and objective, standards for PD-L1 testing need to be established. At a meeting in London in October 2015, a group of experts was brought together to discuss current knowledge about PD-L1 testing and to assess the research that is still required as a priority, in order for reliable and accurate testing to be ensured.

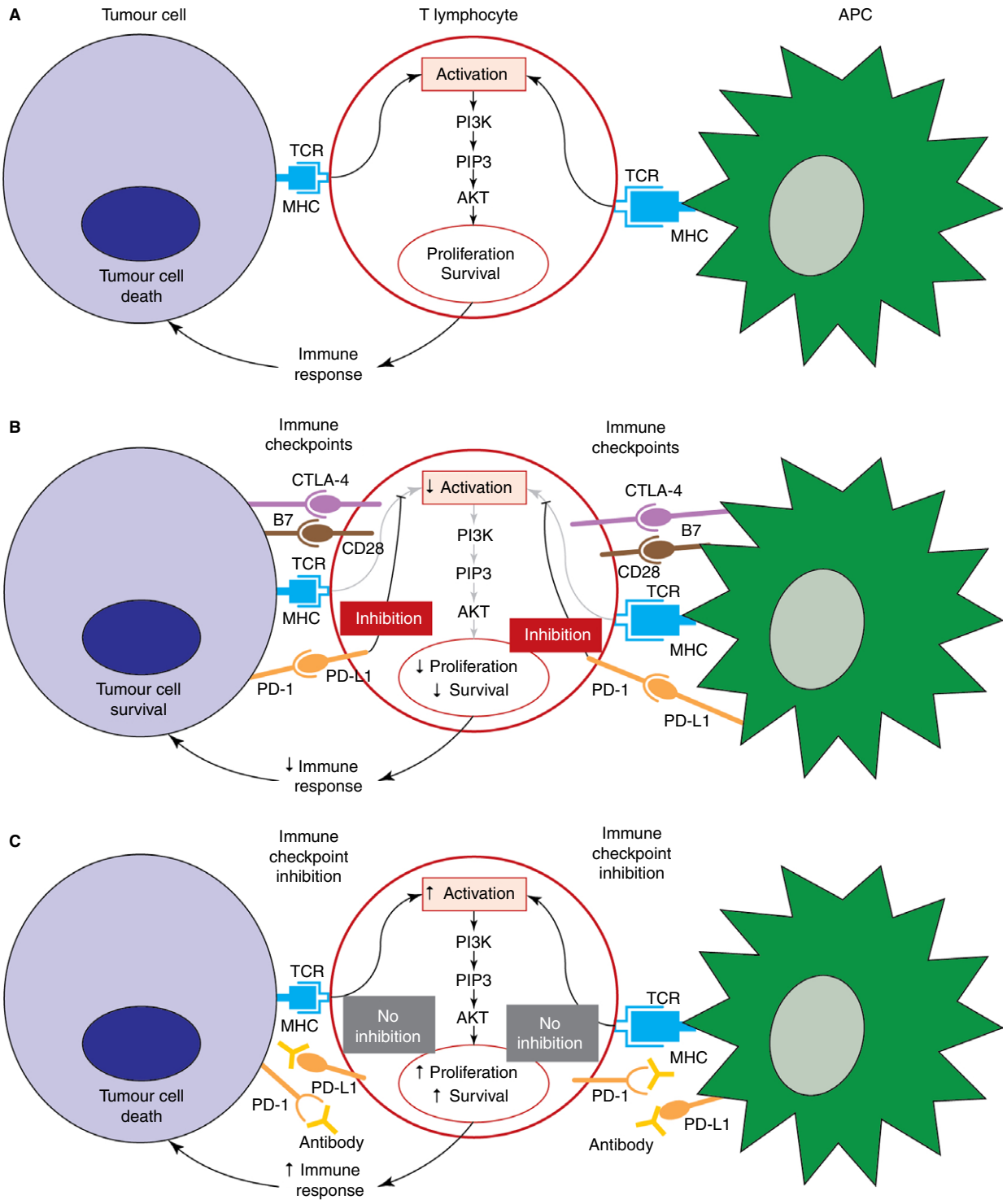

Figure 1. Role of programmed death receptor 1 (PD-1) in cancer immunology. For activation and transformation into immune effector cells, quiescent T cells require stimulation by major histocompatibility complex (MHC) proteins on antigen-presenting cells (APCs). However, uncontrolled stimulation could result in adverse effects on host cells (e.g. manifesting as hypersensitivity reactions). To control these effects, T cells are activated only in the presence of additional signalling from 'co-stimulatory' interactions, whereas activation is inhibited by 'co-inhibitory' interactions. PD-1 is an example of a co-inhibitory receptor, which, when activated by its ligand [usually programmed death ligand 1 (PD-L1) on cancer cells], blocks intracellular signalling along the phosphatidylinositol 3-kinase (PI3K)–Akt pathway. As a result, the T cell is prevented from proliferating or producing cytokines, and the immune response is suppressed.

This article summarizes the findings of that meeting, some of the points from which have been taken up by the Blueprint study proposal, which may provide the answers to some of the questions posed here (http://www.aacr.org/AdvocacyPolicy/GovernmentAffairs/Documents/FDA-AACR-ASCO-Complexities-in-Personalized-Medicine-Blueprint-Proposal.pdf).

Sample collection

SAMPLING METHOD

Acquisition of sufficient lung cancer tissue for examination is the key first step in PD-L1 testing. Several techniques are available, including flexible bronchoscopy, computed tomography (CT)-guided needle biopsy, and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). All of these methods have yields of >85% for lung cancer diagnosis, with minimal complication rates.

A systematic review of CT-guided fine needle aspiration and core needle biopsy showed no differences between the two techniques in terms of diagnostic yield and rates of complications (pneumothorax or haemorrhage).[10] However, only two of the studies included in the analysis were published after 2005, and neither of these was randomized. Few studies have documented the adequacy of samples taken for lung cancer subtyping derived from bronchoscopy, CT-guided biopsy, or aspiration, but complication rates of 17% from CT-guided intrathoracic research biopsy have been reported.[11] In a study of CT-guided lung biopsies taken with a 20-gauge needle before randomization in an NSCLC clinical trial, specimens from 83% of patients had adequate tumour tissue for analysis of the required biomarkers.[12] The rates of pneumothorax and intercostal drainage were 15% and 9%, respectively.

The use of EBUS-TBNA as a primary diagnostic and staging tool for lung cancer has expanded rapidly in recent years.[13] A multicentre, real-world study of 774 patients with known or suspected lung cancer found the sensitivity of this procedure to be 88%, with a diagnostic accuracy of 91%.[14] EGFR mutation testing was possible in 90% of cases in which it was requested. Similarly, in a prospective study of 451 patients undergoing EBUS-TBNA, the sensitivity (87–93%) and procedural tolerance were high, and overall complication rates were low (<9%, mostly minor), regardless of patients' age and performance status.[15] Sufficient tissue was collected for morphological evaluation and EGFR mutation analysis in >97% of cases. Given its favourable safety and efficacy profile,[16] EBUS-TBNA is now regarded as the most useful approach for repeated lung cancer tissue sampling. The suitability of specimens from EBUS-TBNA for assessment of PD-L1 status is currently being investigated in terms of viable tumour cell numbers for interpretation and validation of PD-L1 assays on EBUS-TBNA specimens.

TUMOUR HETEROGENEITY AND EVOLUTION

There is increasing evidence of heterogeneity both within the primary tumour and between primary tumours and metastases. For example, in a study comparing EGFR status in primary lung cancer specimens and lymph node metastases, there was discordance in 17% of cases.[17] Thus, a biopsy from a single site may not be representative of overall tumour biology and burden. It is not yet known whether this phenomenon affects PD-L1 status, although this seems likely.

Techniques such as EBUS-TBNA or CT-guided coaxial biopsy facilitate intratumoral or involved lymph node sampling as a result of deeper core sampling than is obtained with superficial pinch biopsies at bronchoscopy. With additional technologies, such as navigational bronchoscopy in combination with EBUS-TBNA, sampling of the primary tumour and multiple intrathoracic lymph nodes during a single procedure can identify the heterogeneity of regional metastatic disease to a far greater extent than was previously possible. Assessment of TILs is not possible in lymph node samples, and is difficult in cytological tumour samples.

In addition to the tumour heterogeneity present at a given time, tumours can also evolve over time. It is therefore unclear whether the presence of a marker such as PD-L1 in a biopsy taken at the initiation of first-line therapy will remain predictive of treatment response in the second-line setting. However, re-biopsy of tumours in patients with advanced NSCLC is not routinely performed, owing to patient health or unwillingness, or technical limitations. In a recent study of repeated CT-guided biopsy following disease progression after first-line therapy, suitable tissue for molecular analysis was obtained in 80% of cases, and 14% of patients experienced complications.[18] In a multicentre study of 100 patients following treatment for advanced NSCLC, re-biopsy was not possible in 20% of cases, and provided inadequate tumour cells in 26% of cases.[19]

Nonetheless, the data demonstrate that it is possible to perform repeat biopsy with CT or advanced bronchoscopic modalities. A study of the feasibility and clinical utility of re-biopsy in routine practice found that it was useful for guiding treatment in advanced NSCLC in 30% of cases, leading the study's authors to recommend re-biopsy whenever possible.[19]

However, the applicability of these findings to PD-L1 is unknown, and data specific to PD-L1 testing are not currently available.

Pre-analytical considerations

Pathologists are required to provide an increasing variety of ever more complex diagnostic information from small biopsies in NSCLC and other diseases. It is essential to pay attention to pre-analytical considerations, including fixation and sample processing, to ensure the reliability of results. PD-L1 testing should be compatible with other tests required and their analysis.

In some cases, central laboratories may offer all of the necessary testing and provide a useful option. However, centralized testing may be problematic if specimens need to be split and sent to separate laboratories for different tests. Distribution of specimens to distant sites can prove difficult if clinical teams require a short turnaround time. Current guidance for molecular pathology from the European Society for Pathology and the UK Royal College of Pathologists indicates that this choice should be a multidisciplinary decision based on local expertise, need, cost, and tissue availability.[20]

Tissue for PD-L1 testing does not require any special preparation. The key pre-analytical steps are similar to those for other immunohistochemical and molecular tests, and include sample tracking, fixation, tissue processing, sectioning, and tissue prioritization.

SAMPLE TRACKING

The early use of bar-coding is strongly advocated, as this minimizes the risk of sample confusion, especially if the sample needs to be split or sent away, as this could result in patients receiving incorrect treatment. It is also essential that laboratories operate in accordance with ISO15189 to avoid such issues. Nevertheless, misidentification continues to be commonly encountered within External Quality Assessment (EQA) schemes.

FIXATION

Small biopsies fix rapidly in formalin, and there is standardization across pathology laboratories in the use of 10% neutral buffered formalin. To provide optimal fixation, it is good practice to incise larger specimens where possible, respecting resection margins. In the lung, the airways can also be used to inflate specimens with formalin, ensuring that there is no delay in tumour fixation. In general, at least 5 h for biopsies and 24–72 h for surgical excisions is advised. Cross-linking of proteins in the tissue resulting from overfixation can create problems for the penetration of antibody reagents used in both immunohistochemistry (IHC) and molecular pathology.

TISSUE PROCESSING

The use of automated tissue processors is now ubiquitous. These instruments allow exposure of tissue samples to fixative, alcohol dehydration, xylene or equivalent, and paraffin wax, under temperature and pressure (vacuum) control. However, individual departments vary in their exposure time and temperature preferences, which can affect the results of IHC and nucleic acid extraction for molecular pathology. Manufacturers of such instruments should attempt to standardize their methods, and further standardization of processing within histopathology departments would be advantageous.

SECTIONING

Where possible, sections of 3–4 μm should be cut shortly before IHC is performed. Storage of samples for up to 1 week may have no adverse effect on staining results, although further data are required to confirm this. Even though assay manufacturers have shown cut-sample stability of up to 6 months (Dako UK Ltd, Ely), this approach is not recommended, as there may still be tissue degradation and, more importantly, patients are likely to require treatment decisions much sooner.

TISSUE PRIORITIZATION

The immediate need for a patient with suspected NSCLC is to obtain a tissue diagnosis from a suitable biopsy. This is best accomplished by a histopathologist viewing a haematoxylin and eosin-stained section, or preferably a series of sections. Most pathology departments therefore cut a series of sections and stain several at different levels for histopathology, while retaining intervening sections for IHC. If there is morphological evidence of adenocarcinoma or squamous differentiation, IHC is not required unless there is a question regarding the primary site of origin. Where there is no morphological evidence of squamous or glandular differentiation, a limited IHC panel (e.g. p40 and thyroid transcription factor-1) is recommended, with classification according to the World Health Organization criteria for non-resection samples.[21] This should reduce the number of cases classified as 'NSCLC not otherwise specified' to <10%.

We therefore propose that tissue sections for PD-L1 IHC should be taken at the same time as those for diagnostic IHC (if the latter is required) or later for IHC for ALK and other predictive markers (e.g. EGFR and ROS1), according to the preference of the multidisciplinary team. It is important to ensure that sufficient material is left within the block for sections to be cut for mutational analysis. The process is summarized in Figure 2.

Analytical considerations

CHOICE OF BIOMARKER KIT AND AUTOMATED STAINING PLATFORM

Companion PD-L1 IHC assays/kits are available or in development, corresponding to different checkpoint inhibitors for the treatment of PD-L1-positive NSCLC (Table 1). Companion diagnostic assays/kits allow greater standardization of PD-L1 IHC staining, and remove the potential uncertainties or pitfalls associated with laboratory-devised techniques (LDTs). Data from the UK National External Quality Assessment Service for Immunocytochemistry and *In Situ* Hybridization (UK NEQAS ICC & ISH) show that laboratories using standardized assays outperform those using LDTs in ALK IHC assessments for NSCLC.[22] The assays have been developed with corresponding staining methodologies, and are automated platform-specific. Laboratories must adhere to the recommended staining protocols of the manufacturer, as protocol modifications might lead to false-positive or false-negative PD-L1 results. Before the introduction of a new

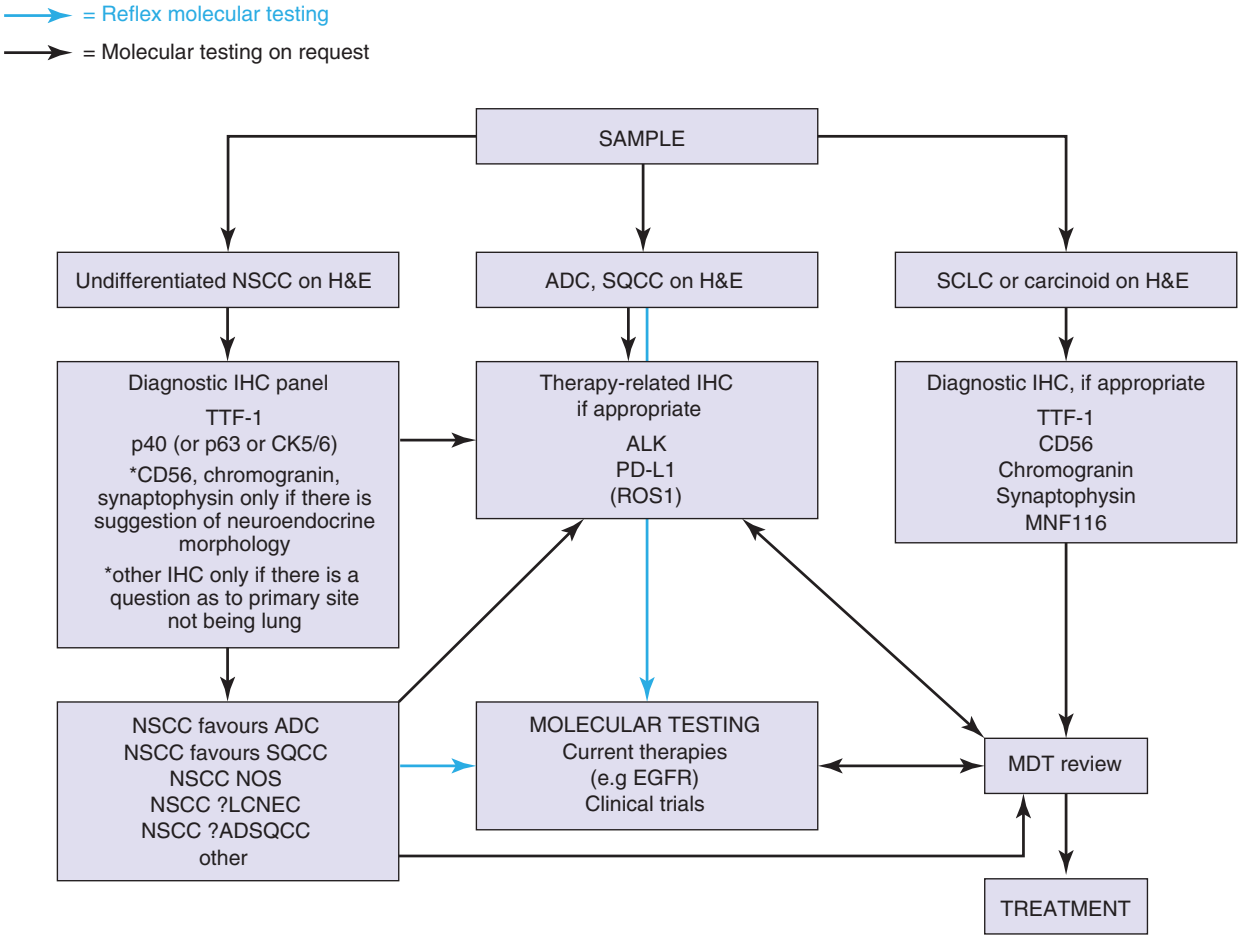

Figure 2. Potential place of programmed death ligand 1 (PD-L1) testing in diagnostic immunohistochemistry (IHC) and the molecular pathology of non-small-cell lung cancer. ADC, adenocarcinoma; ADSQCC, adeno-squamous carcinoma; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; H&E, haematoxylin and eosin; LCNEC, large-cell neuroendocrine carcinoma of the lung; MDT, multidisciplinary team; NOS, not otherwise specified; NSCC, non-small-cell carcinoma; ROS1, c-ros oncogene 1 receptor tyrosine kinase; SCLC, small-cell lung cancer; SQCC, squamous cell carcinoma; TTF-1, thyroid transcription factor-1.

Table 1. Programmed death ligand 1 (PD-L1) kits and platforms available for each anti-programmed death receptor 1 (PD-1)-targeted or anti-PD-L1-targeted agent

Methodology	Kit assay	Automated platform	Checkpoint inhibitor	Target
Kit-based assay	Dako 22C3 pharmDx	Dako Autostainer Link 48	Pembrolizumab (MSD)	PD-1
	Dako PD-L1 IHC 28-8 pharmDx	Dako Autostainer Link 48	Nivolumab (BMS)	PD-1
	SP142: kit form TBC	Ventana: TBC	Atezolizumab (Roche)	PD-L1
	SP263: kit form TBC	Ventana Benchmark platforms (GX, XT, and Ultra)	Durvalumab (AstraZeneca/ MedImmune)	PD-L1
Standalone PD-L1 antibodies*	28-8 (RabMAb): BMS clone available from Abcam			
	E1L3N (RabMAb): Cell Signaling			
	SP142 (RabMAb): Spring Bioscience			

TBC, to be confirmed.
*Not validated for clinical use.

diagnostic test into routine clinical service, laboratories must follow one of two processes:[23]

- Verification of standardized kit assays.
- Validation of LDTs (including antibody dilution, epitope retrieval and detection methods), with robust methodology in an appropriate sample size, in order to ensure reproducibility.

TRAINING AND INTERPRETATION

It will be critical for pathologists and scientists to undertake relevant training on the companion diagnostic assay and its expected staining profile, and the cut-offs associated with the drug under consideration. Interpretive training should incorporate samples showing the full range of PD-L1 IHC staining, including known negative and positive NSCLC cases.

Interobserver variability in PD-L1 staining interpretation should be strictly monitored, with the recommendation that potential interpreters should review a sufficient number of cases to achieve a minimum concordance of 95%[24] (in contrast to US guidelines, in which a concordance rate of 90% is deemed acceptable).

Quality assurance

Quality assurance is a requirement for all UK-accredited clinical laboratories, with many laboratories now undergoing transition from the UK Accreditation Service (UKAS) to the ISO15189 standard. All procedures for verification or validation must be documented in a standard operating procedure, and the clinical laboratory should also consider other aspects of uncertainty of measurement, such as:[25,26]

- The measuring instrument (maintenance and calibration).
- The object being measured (is the measured property stable?).
- The measurement process (tumour size in three dimensions).
- The environment (temperature, air pressure, and humidity).
- Sampling issues.
- The operator's skill and judgement.

CONTROLS

Even though companion assays are standardized and optimized, there may still be batch-to-batch variability with reagents, and unforeseen issues with automated staining platforms. It is therefore recommended that laboratories should include controls alongside their clinical cases being tested for PD-L1, to ensure that the sensitivity and specificity of the test are satisfactory. Ideally, NSCLC controls should be used, showing at least positive and negative PD-L1 expression. The use of controls with staining results close to the decision-making cut-off points is also recommended. Ideally control sections should be cut at the same time as the test material, and should be similarly fixed and processed. Long-term storage of pre-cut control

sections should be avoided. Commercial control samples and cell lines are becoming increasingly available, and these can be used as alternatives to tissue samples. Commercial controls should also be cut onto the same slide as the clinical samples.

EXTERNAL QUALITY ASSURANCE

Any laboratory carrying out clinical PD-L1 IHC testing must take part in an EQA as outlined by ISO15189. An EQA for PD-L1 will provide information on how well a laboratory's assay has worked, and any potential staining issues that may lead to false-positive or false-negative results. The EQA requires continuous participation; it helps laboratories to monitor their staining and interpretive methods and, where required, provides individual feedback to laboratories to improve staining methodologies.

The UK NEQAS ICC & ISH, a not-for-profit organization that develops EQA modules covering numerous areas of pathology, is currently in the planning stages of a pilot PD-L1 EQA. The UK NEQAS ICC & ISH, which is open to laboratories from all countries, monitors UK participants for poor performance, and reports persistent underperformers to the National Quality Assurance Advisory Panel, which makes the final decision on whether a laboratory may continue to perform clinical IHC testing.

AUDIT

The expected PD-L1 positivity rate in the UK is currently unknown, and national data (acknowledging regional variations) should be collected. Individual laboratories must also audit their positivity rates in order to highlight technical issues and the sensitivity and specificity of different batches of PD-L1 assays.

INTERPRETATION

It is important to provide PD-L1 IHC results as part of an integrated report, including the histopathological diagnosis, the results of IHC to type the tumour, and mutation analysis. Given the constraints of existing laboratory information management systems and electronic patient records, this is often a considerable challenge. For PD-L1 IHC, the report should contain the proportion of neoplastic cells staining positively. For one of the drugs in development, the biomarker test is based on the area of tumour infiltrated by PD-L1-positive immune cells, including tumour-infiltrating (non-neoplastic) cells. Current evidence suggests that the intensity of staining is not critical. Figure 3 shows the results of PD-L1 IHC staining.

Responses to this class of drugs have been seen in patients showing all levels of PD-L1 expression, and, for each drug and companion test, the thresholds defining a 'positive' test result are different. It would seem sensible to simplify as much as possible the criteria for considering any individual tumour to be 'positive' or 'negative' for PD-L1 expression. The use of a simple percentage cut-off for expression, irrespective of intensity or other subjective features, is welcome to minimize the number of cases that cross the threshold as a result of technical variability (e.g. owing to differences in staining techniques resulting in variation in intensity). Assays confined to the assessment of neoplastic cells would also be pragmatic. Such an

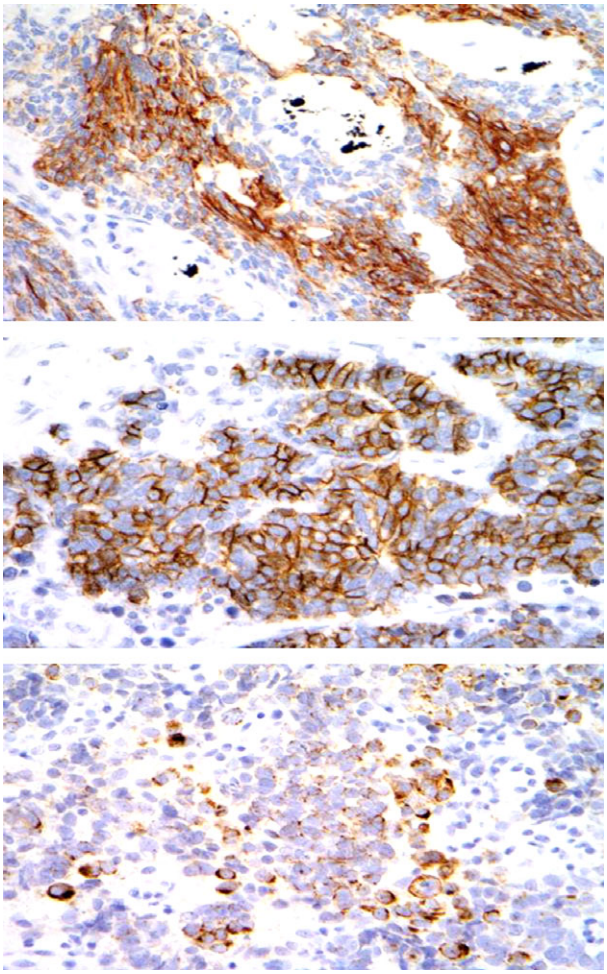

Figure 3. Three fields from the same section of a resected adenocarcinoma of the lung showing expression of programmed death ligand 1 as detected by the Dako 22C3 antibody. The spatial heterogeneity and variable pattern of expression are well shown.

approach should be applicable to both cytology and histology specimens, which is an important consideration given that endobronchial ultrasound-guided aspirates are now increasingly being used in the combined diagnosis and staging of lung cancer. However, it should be noted that cytology samples were never used in the validating clinical trials, so none of the assays is technically validated for use on these types of sample. Recent work has shown that at least three of the companion diagnostic assays available (based on the 28-8, 22C3 and SP263 clones) are technically comparable on the same tissues, whereas an assay based on SP142 was less concordant.[27] We will need more data before any recommendation can be made on use of anything other than a trial-proven assay in association with a drug.

Areas for further research

To ensure that PD-L1 testing is introduced effectively into routine clinical practice, several issues need to be addressed in research, including:

- Relevance of tissue source and sample quality.
- Heterogeneity of PD-L1 expression within the tumour, between primary and metastatic lesions and over time.
- Impact of prior lines of treatment on PD-L1 expression.
- Optimal cut-offs identifying appropriate patient populations for treatment.
- National and regional rates of PD-L1 positivity.
- Reproducibility and concordance of companion diagnostic kits and platforms, including minimum number of cases per year to ensure consistency of interpretation, and applicability to the different drugs available or in development—a cross-industry collaborative project is underway to agree and deliver 'a package of information/data upon which analytic comparison of the various diagnostic assays may be conducted, potentially paving the way for post-market standardization and/or practice guideline development as appropriate'.[28]
- Validation of LDTs.
- Role of TILs and/or staining intensity in interpretation.
- Role of digital pathology.

Conclusions

Immunotherapy for cancer is now a reality. The drugs involved are expensive, and will be used in concert with existing treatment modalities, as well as with other new drugs targeting molecular pathways. To maximize clinical benefits, the challenge is to stratify patients adequately following tissue diagnosis, and PD-L1 IHC may be a requirement for patients with NSCLC. In this article, we have set out a pathway for standardizing PD-L1 IHC as an important first step towards integration of PD-L1 into locally agreed protocols for pathology testing and treatment decision-making. As immunotherapy progresses from research to routine clinical use, there remain considerable areas of uncertainty, and guidance should be updated regularly as new information becomes available.

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The sponsorship provided by MSD reimbursed reasonable travel expenses for members of the Task Group to attend Task Group meetings. MSD did not provide honoraria payments to members of the Task Group in relation to this activity.

MSD did not attend Task Group teleconferences or face to face meetings, or review the article in draft or final form. MSD did not make contact with the Task Group members in relation to this activity.

Author contributions

All authors discussed and agreed on the scope of the article. I. A. Cree, R. Booton, P. Cane, J. Gosney, M. Ibrahim, K. Kerr, R. Lal, N. Navani and A. G. Nicholson wrote the first draft of the article, with editorial support from S. Black at Succinct Medical Communications. All authors reviewed the draft, agreed on the revisions, and approved the final version for submission.

Conflicts of interest

All authors have received honoraria from MSD UK for advisory board meetings; MSD also sponsored writing support for this article. I. A. Cree has also been involved in advisory boards or meetings with GSK Oncology (now part of Novartis), Roche, Lilly, Amgen, AstraZeneca, and Biocartis. C. Lewanski has been an adviser to MSD, AstraZeneca, and Roche Pharmaceuticals. J. Gosney has been a paid adviser to and speaker for AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Lilly & Co., MSD, Novartis, Pfizer, and Roche. A. G. Nicholson has been a paid adviser to AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Lilly & Co., MSD, Novartis, Pfizer, and Roche, and a speaker for AstraZeneca and Lilly and Co.

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