Journal of
Molecular Pathology

MDPI

Review

What Is New in Biomarker Testing at Diagnosis of Advanced Non-Squamous Non-Small Cell Lung Carcinoma? Implications for Cytology and Liquid Biopsy

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Abstract: The discovery and clinical validation of biomarkers predictive of the response of non-squamous non-small-cell lung carcinomas (NS-NSCLC) to therapeutic strategies continue to provide new data. The evaluation of novel treatments is based on molecular analyses aimed at determining their efficacy. These tests are increasing in number, but the tissue specimens are smaller and smaller and/or can have few tumor cells. Indeed, in addition to tissue samples, complementary cytological and/or blood samples can also give access to these biomarkers. To date, it is recommended and necessary to look for the status of five genomic molecular biomarkers (*EGFR*, *ALK*, *ROS1*, *BRAFV600*, *NTRK*) and of a protein biomarker (PD-L1). However, the short- and more or less long-term emergence of new targeted treatments of genomic alterations on *RET* and *MET*, but also on others' genomic alteration, notably on *KRAS*, *HER2*, *NRG1*, *SMARCA4*, and *NUT*, have made cellular and blood samples essential for molecular testing. The aim of this review is to present the interest in using cytological and/or liquid biopsies as complementary biological material, or as an alternative to tissue specimens, for detection at diagnosis of new predictive biomarkers of NS-NSCLC.

Keywords: lung cancer; biomarkers; cytology; liquid biopsy; diagnosis

Citation: Hofman, P. What Is New in Biomarker Testing at Diagnosis of Advanced Non-Squamous Non-Small Cell Lung Carcinoma? Implications for Cytology and Liquid Biopsy. *J. Mol. Pathol.* **2021**, *2*, 147–172. https://doi.org/10.3390/jmp2020015

Academic Editor: Giuseppe Banna

Received: 23 April 2021
Accepted: 28 May 2021
Published: 4 June 2021

1. Introduction

In recent years, therapeutic strategies for advanced-stage non-squamous non-small-cell lung carcinoma (NS-NSCLC), in particular lung adenocarcinoma, have evolved in a dramatic way due to the development of targeted therapies and immunotherapies that have significantly improved the survival of these patients [1,2]. Therefore, a number of molecular therapeutics rapidly obtained marketing approval from the Food and Drug Administration (FDA) in the USA and by the European Medicines Agency (EMA) in Europe (Table 1). Other treatments are being evaluated in clinical trials and the results already indicate a strong likelihood of novel treatments for daily practice [3–7] (Table 1). As a consequence, international recommendations have been issued for evaluation of biomarkers at diagnosis of advanced-stage NS-NSCLC [8–11]. However, the progressive increase in the number of biomarkers raises of the following questions. (i) Which technique(s) should be used for detection, while considering the delay in transmission of the results that needs to be compatible with administration of first-line treatment? (ii) What is the cost for these different tests? (iii) On what type(s) of biological sample(s) should biomarker detection be made, knowing that tissue specimens are smaller and smaller in thoracic oncology [4,12,13]?

Table 1. Current recommended, coming soon, and potential future genomic biomarkers to be looked for at baseline in non-squamous non-small-cell carcinoma.

EMA Approved	Coming Soon	Investigational
EGFR	*RET*	*NRG1*
ALK	*MET*	*FGFR1*
ROS1	*KRAS G12C*	*SMARCA4*
BRAFV600	*HER2*	*NUT*
NTRK		Others (*MEK*, *PI3KCA*, *STK11*, etc.)

An appropriate daily routine practice must adapt algorithms for testing to provide a robust diagnosis, irrespective of the patient and the available biological specimens [14–33]. However, the pathologist is faced with different strategies and decisions, while taking into consideration the size, the quality and quantity of the sample, and the percentage of tumor cells. In addition to providing a diagnosis, the pathologist must evaluate the need to prescribe not only immunohistochemical analyses but also molecular tests. Therefore, the clinical pathologist is always on the front line for making decisions (go/no go) for further analyses. The molecular tests can be performed in a targeted way, often sequential, or with next-generation sequencing (NGS) approaches [34–39]. The increasing number of genes for analysis has created methodological constraints that depend on the nature of the biological specimen [11,40]. The use of cytological (fine-needle aspiration, bronchial aspiration, bronchoalveolar lavage, etc.) and/or liquid samples (blood, pleural effusion, cerebrospinal fluid, etc.) must allow detection of all required biomarkers for targeted therapy or immunotherapy in thoracic oncology [18,40–43]. This review presents the biomarkers that have been identified in the domain of thoracic oncology that can be potentially detected using cytological materials and/or liquid biopsies taken at diagnosis of NS-NSCLC. First, we will briefly discuss the already well-known genomic alterations present on different genes (*EGFR*, *ALK*, *ROS1*, *BRAF*), which can be targeted by different drugs in routine clinical practice, before focusing on major new molecular therapeutic targets present in other genes (*NTRK*, *RET*, *MET*, *KRAS*, *HER2*, *NRG1*, *SMARCA4* and *NUT*).

2. Biomarkers Assessed at Diagnosis with Cytological Samples and/or Liquid Biopsies Obtained from Advanced Non-Squamous Non-Small-Cell Lung Cancer Patients

For therapeutic care of advanced-stage NS-NSCLC at diagnosis it is recommended to evaluate the status of at least five genomic biomarkers (the "big five": *epidermal growth factor receptor* (*EGFR*), *anaplastic lymphoma kinase* (*ALK*), *v-ros avian UR2 sarcoma virus oncogene homolog 1* (*ROS1*), *v-raf murine sarcoma viral oncogene homolog B1* (*BRAF*), and *neurotrophic tyrosine kinase* (*NTRK*)) and the expression of programmed death-ligand 1 (PD-L1). In most countries, including France, the detection of a genomic alteration in one of these genes leads to treatment with osimertinib (*EGFR* mutation); alectinib, brigatinib, or lorlatinib (*ALK* rearrangements); crizotinib (*ROS1* rearrangements); the association dabrafenib/trabetinib (*BRAFV600 mutation*); or larotrectinib or entrectinib (*NTRK* rearrangements). The tests can be performed with cytological and/or liquid samples but their sensitivity, and even their specificity, are generally more variable than tests with tissue samples [44–48]. The evaluation of PD-L1 can be performed and validated with cytological samples but has not been validated in daily routine with blood samples [41,49–52]. Aside from the "big five" biomarkers, the arrival of other biomarkers for short- (genetic alterations in *proto-oncogene tyrosine-protein kinase receptor Ret* (*RET*) and *MET proto-oncogene receptor tyrosine kinase* (*MET*)], mid- (genetic alterations in *v-Ki-ras2 Kirsten rat sarcoma 2 viral oncogene homolog* (*KRAS*), *human epidermal growth factor receptor 2* (*G12CHER2*), and *Neuregulin 1* (*NRG1*)), or long-term detection (genetic alterations in *SWI/SNF-related*, *matrix-associated*, *actin-dependent regulator of chromatin*, *subfamily A*, *member 4* (*SMARCA4*), *nuclear protein in testis* (*NUT*), and other genes) has to involve validation on cytological and/or blood samples (Table 1). Thus, the choice of first-line targeted therapy based on the detection of these biomarkers with

cytological and liquid biological samples is and could be a complementary approach to tissue biopsies [42,44].

2.1. EGFR, ALK, ROS1, BRAF, and NTRK: What Is New for the "Big Five" When Using Cytological and Blood Samples?

2.1.1. EGFR

EGFR mutations have been detailed in many reviews and publications in the past few years and will be not detailed here. These mutations are known to be more frequently detected in nonsmoker patients and in women, but this incidence varies according to the population [53,54]. Therefore, *EGFR* mutations are detected in 10% to 19%, 15% to 20%, 27% to 35%, and 35% to more than 48%, in Caucasian, African and Middle East, Hispanic, and Asian patient populations, respectively [53–57]. Despite some discrepancies of results in a few studies, most research has shown that the frequency of *EGFR* mutations in African Americans is not distinct from NS-NSCLC in northern and southern Caucasian patients [58–60]. Finally, the incidence found in NS-NSCLC patients of Indian ethnicity is around 23% to 30% [61,62]. At baseline, driver mutations or more rarely resistant mutations can be targeted by different tyrosine kinase inhibitors (TKIs), notably the third generation of TKIs such as osimertinib [63]. These genomic alterations are detectable on cytological samples and in liquid biopsies (LB) and are certainly the first mutations that are looked for in routine clinical practice for patients in care [63]. In this regard, many targeted sequencing methods, allowing for results in a short amount of time from cytological or blood specimens, have been used in many hospitals [64–66]. More recently, NGS methods have developed from these specimens, notably for *EGFR* status evaluation at baseline [67]. NGS approaches are of strong interest in order to detect different genomic alterations associated in genes other than *EGFR*, which may explain, at least partially, some primary resistance of TKIs targeting *EGFR* mutations [68]. It will be certainly mandatory soon to evaluate the landscape of the different genomic alterations present in several genes and to assess other biomarkers in situ for a better prediction of therapeutic response to medications targeting *EGFR* mutations or to alternatively provide immunotherapy to these patients [68,69]. It is noteworthy that these NGS methods will be applied not only in the late stages but also in the early stages of NS-NSCLC, which would mean patients receive adjuvant TKIs according to their *EGFR* status [70]. In this context, cytological and blood samples will be certainly more and more used in daily practice for NGS methods.

2.1.2. ALK

ALK rearrangements are present in 2% to 6% of NS-NSCLC patients according to the studies and the frequency slightly varies in the different populations [53,71]. These genomic alterations are sensitive to different medications, notably to the new generation of TKIs (alectinib, lorlatinib, and brigatinib) [72]. Moreover, it is crucial to detect an *ALK* fusion if a patient needs to be treated via immunotherapy due to an association of non-efficacy and of treatment toxicity of the immune checkpoint inhibitors (ICIs) in cases of *ALK*-positive tumors [73]. *ALK* status at baseline can be assessed not only in tissue biopsy but also in cytological specimens and in blood samples, notably on circulating free nucleic acids [47,67,74]. However, different studies demonstrated that the evaluation of *ALK* status can be made in circulating tumor cells at baseline. *ALK* status can be assessed in cytological samples using ALK immunocytochemistry and *ALK* fluorescence in situ hybridization (FISH), which can be used at the same time for *ROS1* status evaluation [75–79]. At diagnosis, the detection of *ALK* fusion in plasma is be possible, but the sensitivity of this detection in comparison with matched tissue samples is variable according to the different studies [46,67,74]. RNA NGS can be used from cytological samples for *ALK* status assessment and identification of the different partners of *ALK* fusion [75,80]. Moreover, other technologies, such as multiplex technology based on RNA hybridization, are able to detect *ALK* in RNA purified from tissue and also from the cytological specimen, in addition to being able to look for associated genomic alterations of interest [81,82]. *ALK*

translocated lung cancers are a heterogeneous group of tumors, and it is now pivotal to evaluate *ALK*-positive NS-NSCLC at baseline in the context of their genomic background in order to more clearly predict the behavior of tumors before targeted therapy [72,82]. However, the robustness of the results greatly depends on the quantity and on the quality of the RNA, which can be significantly degraded depending on the preanalytical phase (type of fixative, time of fixation, type of cytological sample, e.g, smears or cytoblocks) [75].

2.1.3. ROS1

ROS1 rearrangements are detectable in 1% to 2% of NS-NSCLC patients according to the studies and the populations [83]. These genomic alterations are sensitive to some targeted therapies, mainly involving crizotinib, but some resistant mechanisms can be present during the tumor progression, leading to the possibility of other targeted therapies at baseline, such as those involving entrectinib [84], being effective. *ROS1* fusion can be assessed in tissue biopsy using ROS1 IHC, but positive results have to be confirmed by *ROS1* FISH or by NGS [75,78,83,85]. More exceptionally, ROS1 ICC and *ROS1* FISH can be realized in cytological specimens [75,77]. RNA NGS, notably through the use of gene fusion panels that combine the possibility to detect *ALK*, *RET* or *NTRK*, can be used from cytological materials [83]. In plasma samples, *ROS1* rearrangement can be assessed using some multiplex RT-PCR method or by using NGS [80].

2.1.4. BRAF

BRAF mutations are detectable in different proportions in NS-NSCLC patients, according to research, and these results included not only the BRAFV600 mutations (between 2% to 3% in Caucasians) but also the non-*BRAFV600* mutations (between 5% to 8%) [53]. The *BRAFV600* mutations can be targeted by some *BRAF* inhibitors and the dabrafenib trametinib association [86]. The frequency of *BRAFV600* mutations seems lower in Hispanic and Asian patients than in Caucasians [53,87]. *BRAFV600* mutations can be detectable in tissue biopsy and in cytological samples using RT-PCR and V600E IHC/ICC approaches or via NGS [88,89]. In plasma samples, *BRAFV600* mutations can be detectable via RT-PCR or NGS [67,90].

2.1.5. NTRK, a Very Recently Recommended Biomarker, Is One of the "Big Five"

Fusions in *NTRK* can be detected in different types of solid tumors, but with a variable frequency [91–93]. Thus, some fibroblastic and thyroid tumors in children and some breast and salivary gland carcinomas have a higher incidence of this genomic alteration [91,92]. In contrast, the incidence of *NTRK* fusions in NS-NSCLC patients is very low, less than 0.01% to 1% depending on the study and population [94–97]. In general, it concerns the youngest patients without distinction of sex in Caucasians, and, often but not always, in nonsmokers [94]. Despite this low frequency in NS-NSCLC patients, it is essential today to look for fusions in *NTRK* knowing the efficacy of targeted therapy for this molecular alteration [98–106]. Thus, this should now be systematically investigated in patients at diagnosis of NS-NSCLC for administration of first-line treatment [11]. Entrectinib and larotrectinib have recently been authorized by the FDA and the EMA [107,108]. This raises the question of which technique(s) and biological sample(s) should be used for initial systematic evaluation of these very rare fusions in thoracic oncology [109]. At the moment, most of the major studies use tissue samples for *NTRK* status assessment [109–111]. However, detection can be possible with cytological samples and even liquid biopsies [109,112–115]. Several techniques of detection have been developed, including immunohistochemistry (IHC), molecular biology approaches (NGS and RT-PCR), and multiplex digital color-coded barcode technology on tissue sections [11–124]. Depending on the sensitivity and specificity of these techniques and on the biological samples used, these methods can be challenging [125]. Some studies have demonstrated interest in using Trk IHC knowing the anti-Trk antibodies are pan-Trk (anti-NTRK1, 2, 3) [109,110,126–129]. The most commercially available pan-Trk clones are A7H6R (Cell Signaling Technologies) and EPR17341

(Abcam) [109,126–129]. Anti-Trk IHC merits several comments: (i) the sensitivity and specificity of the clones vary according to the study, (ii) knowing that incidence of this fusion in lung cancer, IHC with anti-Trk antibodies may use up biological material that could be used for some alternative approaches, notably NGS, and (iii) the cost can be substantial if IHC is used systematically since the cost of the time of the technician and of pathologist must be included, too [110,117,125,126,130]. IHC must also evaluate the status of *NTRK* on cytological samples, but in daily practice this may not be adequate. The molecular techniques include fluorescence in situ hybridization, targeted or multiplex RT-PCR, DNA- or RNA-based NGS, and analyses using NanoString technology on tissue sections [109,119,121]. Depending on the quality and quantity of the nucleic acids extracted from the sample, false negative results can be obtained [78,81,109,119,121]. Depending on the case, these approaches could be performed with cytological samples, but only a few studies in this area have been performed to date and studies comparing cytological and tissue samples are strongly needed [109,112–115]. The detection of *NTRK* fusions can also be envisaged with a liquid biopsy, but the sensitivity of such an approach is still unknown and needs to be determined.

2.2. Biomarkers Just Beyond the "Big Five" in 2021

2.2.1. RET Fusions

Depending on the patient's ethnicity and technique of detection, fusions in *RET* have been identified in 1% to 2% of NSCLC Caucasian patients and up to 9% in patients from Asia [131–133]. They occur in adenocarcinomas and, exceptionally, in adenosquamous and large-cell carcinomas [134,135]. These cancers are often found in nonsmokers and younger patients, with a slightly higher incidence in women, and sometimes in tumors of small size, frequently at the N2 stage at diagnosis [136,137]. *RET* rearrangements tend to be mutually exclusive with *EGFR* and *KRAS* mutations and *ALK* or *ROS1* rearrangements and can be associated with a low tumor mutation burden (TMB) and a low level of PD-L1 expression [138]. Since the identification of fusions in *RET* in lung cancer in 2012, the number of partners of these fusions has increased [137,139]. The most frequent partners occur in *KIF5B* and *CCD6*, which represent around 60% and 20% of cases, respectively [137]. Different therapeutic medications targeting *RET* fusions have been developed, and, to date, selpercatinib and pralsetinib medications are proposed while waiting for marketing approval by the FDA and EMA [140–145]. However, testing for these fusions will now become systematic at diagnosis for all patients presenting with advanced-stage NS-NSCLC, knowing that patients with *RET* fusions do not generally respond well to immune checkpoint inhibitors (ICIs) [146–149]. Several techniques have been and are being used for detection of *RET* fusions, but their sensitivities vary and so they have gradually been abandoned [132,150]. Thus, IHC is no longer recommended, and FISH is used less and less, notably for lung cancer [151]. Targeted RT-PCR approaches are no longer used and have been replaced by multiplex RT-PCR methods as well as by DNA- and RNA-based NGS or even multiplex analytical techniques on the NanoString platform [136,150–153]. The major limitation of DNA-based NGS lies in the absence of information into effective transcription of the rearranged *RET* gene [113]. This approach presents a problem for *RET* rearrangements since they have an unusual breakpoint in *RET* or have a fusion partner that has never been previously characterized or identified [154]. RNA NGS analyses are certainly the most recommended for *RET* fusion detection due to their sensitivity and specificity [154]. However, if the amount of RNA extracted from tissues or cells is low or if, due to the formalin fixative, RNA is degraded, the RNA NGS approach has it limits. Moreover, depending on the type of NGS sequencing technique, the detection of fusion partners concerns only those known and targeted by the panel (amplicon technique) or detection of all the fusion partners (hybrid capture technique). These different techniques can be certainly applied to cytological specimens obtained in thoracic oncology. Finally, it is also possible to detect *RET* fusions with plasma free-circulating nucleic acids, but to date

the sensitivity of the NGS techniques with blood samples is lower than that obtained with NGS analyses of tissues [155,156].

2.2.2. MET Mutations

Mutations in *MET* on exon 14 are present in less than 2% of lung adenocarcinomas [157]. As for *EGFR*, nonsmokers are overrepresented in *MET*-driven NSCLC cases [157]. However, a greater percentage of patients with either a *MET* amplification or alteration in exon 14 are smokers compared with the majority of other driver alterations [157]. *MET* gene aberration via exon 14 skipping has become an important therapeutic target of lung adenocarcinomas and other histological subtypes such as lung sarcomatoid carcinomas [158–160]. In the short-term, a number of medications (tepotinib and capmatinib) will certainly be used as first-line therapy as soon the FDA and EMA give marketing approval [158,159]. Thus, mutations in *MET* on exon 14 will soon be systematically examined at diagnosis of advanced-stage NS-NSCLC. There is a need to identify the oncogenic role of each type of *MET* alteration and to standardize the diagnostic approach [161]. *MET* exon 14 alterations have been shown to act as oncogenes and to be potentially actionable regardless of gene amplification. Indeed, *MET* amplification alone appears to correlate less strongly with the response to *MET* blockade, whereas only high amplification, excluding polysomy, appears to potentially drive the malignant phenotype and to be predictive of meaningful clinical benefit of targeted treatment. The molecular detection of *MET* on exon 14 skipping most often is achieved with DNA- or RNA-based NGS. However, DNA sequencing can only detect a genomic variant that alters or removes a splicing site. Conversely, RNA sequencing detects the fusion of exon 13 to 15 because this is the convergent result of any altered splicing mechanism or deletion. In addition to pre-analytical considerations, such as the degradation of RNA, the sensitivities of amplicon-mediated DNA-based approaches and hybrid capture RNA-based assays appear to differ [109,119]. Moreover, the probe in amplicon-mediated DNA-based approaches may not cover a sufficient region of interest [119]. Mutations in *MET* can be detected with cytological samples in lung cancer patients but also with liquid biopsies [155]. Currently, comparative studies from tissue and cytological samples or from tissue and blood samples are missing.

2.3. Biomarkers in the Starting Block That Should Come Soon

2.3.1. KRAS G12C Mutations

Mutations in *KRAS* are the most frequent mutations in NS-NSCLCs, in particular for lung adenocarcinomas [162]. The incidence of these mutations varies with ethnicity as they are found in 25% to 35% of Caucasian, 10% to 13% of Asian, and 10% to 18% of Hispanic patients [55,56,87,95,162–167]. Globally, the frequency of *KRAS* mutations in African American patients is not distinct from Caucasians [58,59]. Mutations in *KRAS* are often associated with other mutations, mostly mutations in P53 [122]. The association of mutations in *KRAS* and *serine threonine kinase 11STK11*) confers poor prognosis [164]. Several factors have been found to be often associated with these mutations, including male sex, advanced age, and a specific histological subtype of adenocarcinoma, but none have yet been confirmed to date [164]. A number of subtypes of *KRAS* mutations exists (in particulier *KRASG12C*, *KRASG12D*, and *KRASG12V*), but the most frequent is *KRASG12C* [162]. The reported impact of the mutation in *KRAS* on prognosis varies according to the studies [164,166,168]. Indeed, the worst prognosis seems to be associated with the presence of this mutation, nonetheless this has been questioned in some studies [168]. A lower TMB is associated with a *KRASG12D* mutation than with other subtypes of mutations [169].

For a long time, no targeted molecular therapy was available for *KRAS* mutations, but recently a personalized treatment has been made available [170]. To date, the main target is the *KRASG12C* mutation. Different therapeutic medications, notably sotorasib and adagrasib, are being evaluated and may be swiftly proposed to patients with tumors presenting this mutation, considering the recent excitement of many investigators in this domain [171–195]. This may soon be mandatory in the detection of the different

subtypes of *KRAS* mutations in routine clinical practice. In this context, it has been recently demonstrated that the prognosis of patients having surgery for early-stage NS-NSCLC showing a *KRAS G12C* mutation had more recurrence than in cases of other *KRAS* mutation subtypes or *KRAS* wild-type tumors, thus opening the door in the future for potential adjuvant therapy targeting *KRAS G12C* [196]. These assessments can be done with tissue biopsies but also with cytological samples obtained, for example, via fine-needle or bronchial aspiration [31]. These mutations can also be detected with cell-free DNA from plasma [197]. Detection can be performed with targeted RT-PCR or NGS [197]. The somatic mutations in *KRAS* must be distinguished from constitutional mutations in *KRAS* that are associated with clonal hematopoiesis, since the latter can also be detected with analyses performed with liquid biopsies considering the frequent high amount of circulating germline DNA [198–201]. It is also important to exclude the presence of other cancers associated with a *KRAS* mutation (in particular colon or pancreatic adenocarcinomas), which can release mutated somatic DNA into the blood [198–201].

Mutations in *KRAS* are often associated with an increase in the expression of PD-L1 on tumor cells and with a good response to treatment with anti-PD1/anti-PD-L1 medication [202–204]. Therefore, in the case of first-line treatment, a therapeutic strategy targeting *KRASG12C* can be restricted to patients with tumors expressing PD-L1 on less than 50% of tumor cells. The association of inhibitors targeting the *KRASG12C* mutation with ICIs may also be evaluated [205]. Other therapeutic molecules are being studied, such as inhibitors of mTOR, IGF1R, fatty acid synthase (FASN), or molecules targeting the metabolism of glutamine [206–208]. *KRAS* mutations can also be associated with mutations known to induce resistance to immunotherapy, such as mutations in *STK11* and/or *Kelch-like ECH-associated protein 1*(*KEAP1*), which should be examined simultaneously using NGS [209–219]. Thus, in the presence of these co-mutations, specific inhibitors targeting *KRASG12C* could be considered and given instead of immunotherapy with anti-PD1/PD-L1 medication. However, interestingly, some studies have shown that mutations in *STK11* are less frequent in *KRAS* mutated tumors than in wild-type *KRAS* tumors [220]. It should be noted that, despite the association of these mutations, a rare number of tumors are still sensitive to ICIs [221,222]. Finally, primary or acquired mechanisms of resistance to *KRASG12C* inhibitors have been described and should certainly be researched systematically in the future using NGS approaches [223–227].

Therefore, evaluation at diagnosis of the different mutations in *KRAS* and more specifically the *KRASG12C* mutation with cytological samples and/or liquid biopsies will soon become mandatory. The cytological samples should be used to examine, in parallel, different alterations in other genomic targets (particularly in *EGFR*, *ALK*, *ROS1*, *BRAF*, *NTRK*, *RET*, and *MET*) but also to evaluate the expression of PD-L1 on tumor cells [41]. Searching for mutations in *STK11* and *KEAP1* will also appears to be more and more useful since they are often synonymous with resistance to immunotherapy.

2.3.2. HER2 Mutations

HER2 overexpression is found in patients with different solid tumors, including NSCLC [228]. In NS-NSCLC, the mutational frequency in *HER2* occurs in 0.9% to more than 2% of Caucasian patients, but is higher, up to 5%, in Asian patients [97,229,230]. The presence of *HER2* mutations is defined by a molecular subset of NSCLC with specific clinical-pathological features. These tumors occur in a higher frequency in Asian populations, women, nonsmokers, and in an adenocarcinoma histology even with bronchioalveolar features, a high morphological grade, TTF-1 positive staining, and a peculiar clinical presentation (disseminated lung nodules and tumor excavation), but they seem to have a similar survival compared with other molecularly defined cohorts [231,232]. Despite the higher prevalence in these specific subgroups of patients, *HER2* mutations may be found too in men and heavy smokers. Finally, it seems that a high incidence of brain metastases is detected at diagnosis and on tumor progression in patients having a *HER2* mutation [233].

Several therapeutic medications targeting *HER2* mutations have been developed for lung cancer [234–242]. Notably, it was recently reported that trastuzumab deruxtecan achieved a clinically significant tumor response in patients with HER2-mutant-advanced NS-NSCLC whose disease had progressed following one or more previous systemic therapies (chemotherapy or immunotherapy with immune checkpoint inhibitors against PD-1/PD-L1) [237,240] Thus, the search for these mutations either with tissue or cytological samples, or liquid biopsies, may soon become indispensable, too, at diagnosis of advanced-stage NS-NSCLC. Several approaches can be used to evaluate the status of *HER2* [243,244]. It seems that using HER2 IHC or *HER2* FISH will be not adequate methods in tissue and cytological sample tests, notably due the low frequency of *HER2* mutations in NS-NSCLC. Given the increasing number of genes for analysis and for precision medicine in these patients, the most appropriate method to assess *HER2* status from cytological material and/or liquid biopsies will be certainly DNA- or RNA-based NGS.

2.4. What about Other Biomarkers of Interest?

2.4.1. NRG1 Fusions

Fusions in *NRG1* have been identified and could soon become molecular therapeutic targets [245]. These fusions are present on a certain number of solid lung cancers [246,247]. According to the literature, the incidence is estimated to be low, between 0.1% and 0.4% of NS-NSCLC patients [246,247]. A number of partner fusions exist, where *CD74-NRG1* has emerged as the most frequently reported in *NRG1* rearranged lung tumors [248]. It is interesting to note that fusions in *NRG1* are present in more than 5% of a histological subtype of lung adenocarcinomas, invasive mucinous lung adenocarcinomas [249]. Clinical trials targeting fusions in *NRG1* are presently being evaluated [249]. Indeed, existing ErbB-targeted treatments have potential as targeted therapies for patients with tumors harboring *NRG1* fusions [245].

The detection of these fusions is presently performed with NGS approaches and essentially using RNA sequencing [133,249]. Detection can be performed with tissue biopsies, but certainly with cytological specimens and cell-free tumor nucleic acids in plasma [246]. However, currently, no studies have compared the sensitivity and specificity of the methods for *NRG1* fusion detection with different types of biological material.

2.4.2. SMARCA4 Mutations

A relatively new type of thoracic cancer, in particular lung cancer, with a poor prognosis has been identified to have mutations in *SMARCA4* [250–258]. These mutations have been found in about 5% to 10% of NSCLC patients, mostly NS-NSCLC patients [259]. These mutations are mutually exclusive, with genomic alterations in *ALK*, *ROS1*, *MET*, and *RET* [260]. However, co-mutations in *KEAP1*, *STK11*, and *KRAS* are more frequent in *SMARCA4*-mutated tumors [261]. A few therapeutic medications targeting these mutations are under development, mostly tested in vitro but some are being evaluated in clinical trials, too [259,262–266]. ICIs have been found to be efficacious in patients with *SMARCA4*-mutated tumors [267–269]. However, cases of hyper progression of tumors after administration of ICIs have been reported, too [270].

Mutations in *SMARCA4* constitute a family of mutations present in the SWI/SNF complex, in which other mutations exist, including mutations in *SMARCA2* [271]. Morphological and phenotypical characteristics can point sometimes to such mutations, since these cancers can contain rhabdoid cells or even poorly differentiated cells associated with islets of epidermoid cells [250,251]. One of the key diagnostic elements is the absence of expression in the majority of cases of TTF1 on tumor cells [250,251]. Thus, all the lung adenocarcinomas that do not express TTF1 must be examined for mutations in *SMARCA4*. In this context, IHC with anti-BRG1 antibodies that show the loss of expression of BRG1 in the nuclei of tumor cells but expression in the nuclei of lymphocytes confirms the diagnosis [272–275] (Figure 1). Indeed, when a cytological sample from a patient with lung cancer is negative for TTF1 and BRG1, a mutation in *SMARCA4* must be sought and confirmed

using molecular biology approaches, mainly NGS [275] (Figure 1). These mutations can be detected with NGS not only on tissue biopsies but certainly on cytological samples and liquid biopsies, too [259].

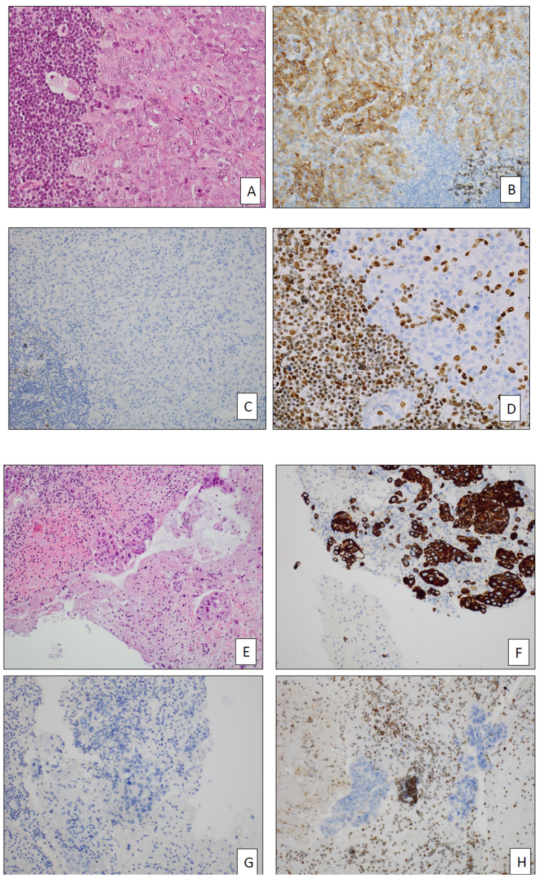

Figure 1. *SMARCA4*-mutated lung carcinoma. Tissue (**A**–**D**) and cytological (**E**–**H**) samples from the same patient. (**A**–**D**) Transthoracic core biopsy. (**A**) Proliferation of a poorly differentiated carcinoma (hematoxylin eosin, magnification × 200). (**B**) Expression of cytokeratins (anti-pancytokeratins antibody, immunoperoxidase, magnification × 200). (**C**) Absence of TTF1 expression on tumor cells (anti-TTF1 antibody, immunoperoxidase, magnification × 200). (**D**) Tumor showing an absence of BRG1 expression on tumor cells but with a strong expression of BRG1 on lymphocytes (anti-BRG1, ab4081 clone, immunoperoxidase, magnification × 200). (**E**–**H**) Endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration. (**E**) Different size of tumor cell nests without differentiation (hematoxylin eosin, magnification × 200). (**F**) Strong expression of cytokeratins (anti-cytokeratin 7 antibody, immunoperoxidase, magnification × 200). (**G**) Absence of TTF1 nuclear staining in tumor cells (anti-TTF1 antibody, immunoperoxidase, magnification × 200). (**H**) Absence of BRG1 staining in nuclei tumor cells associated with BRG1 expression in lymphocytes (ab4081 clone, immunoperoxidase, magnification × 200).

2.4.3. NUT (Nuclear Protein in Testis) Rearrangements

Nuclear protein in testis (NUT) carcinomas are very rare, notably among lung cancers, but are very aggressive tumors [276–282]. These tumors are more frequent in pediatric populations, in particular tumors that develop on the median anatomical axis above the diaphragm [253,283,284]. Histological examination shows poorly differentiated carcinoma cells with a mesenchymal-to-epithelial transition phenotype [285] (Figure 2). Rare cases of squamous cell carcinomas showing rearrangement in *NUT* have been reported [286]. These tumors have chromosome rearrangements in the *NUT* gene on chromosome 15 [287]. In 70% to 78%% of cases, a translocation t (15;19) subsequent to fusion of *NUT* with bromodomain-containing protein 4 (BRD4) on chromosome 19 occurs [287,288]. Other rarer partners,

including BRD3 (15%) and NSD3-NUTM1 (6%), have been described [287,288]. While very rarely diagnosed, the number of *NUT* lung cancers may be underestimated [286,289–291]. Thus, diagnosis can be made with IHC using anti-NUT antibodies that stain the nucleus of tumor cells [292–294] (Figure 2). The result can be confirmed with a FISH analysis using probes against *NUT* or even better with NGS to also identify a fusion partner [295–297]. Diagnosis of *NUT* carcinoma can be performed with cytological material [298] (Figure 2). In this situation, the sample often contains many poorly cohesive tumor cells or, conversely, more cohesive tumor cells with small- or intermediate-sized nuclei with a single nucleolus within fine or fragmented granular chromatin [298,299] (Figure 2). The size of the nucleus is about twice that of the nucleus of a lymphocyte [298]. The cytological images are often rather similar to those described for small-cell lung carcinomas or poorly differentiated carcinomas [298,299]. Another differential diagnosis must be considered for an exceptional primitive lung Ewing sarcoma, too [298]. *NUT* carcinomas express cytokeratins (Figure 2) and P63 but are often negative for neuroendocrine markers and TTF1 [300]. However, some rare tumors can nonetheless be positive for TTF1, chromogranin (Figure 2), synaptophysin, or P40 or be negative for P63 [300–303]. Finally, *NUT* carcinoma can be identified with cytological samples using anti-NUT antibodies and confirmed by NGS [298,304] (Figure 2). Even if to the best of our knowledge no *NUT* lung carcinoma has been currently diagnosed using a liquid biopsy, this may be feasible in theory using NGS approaches.

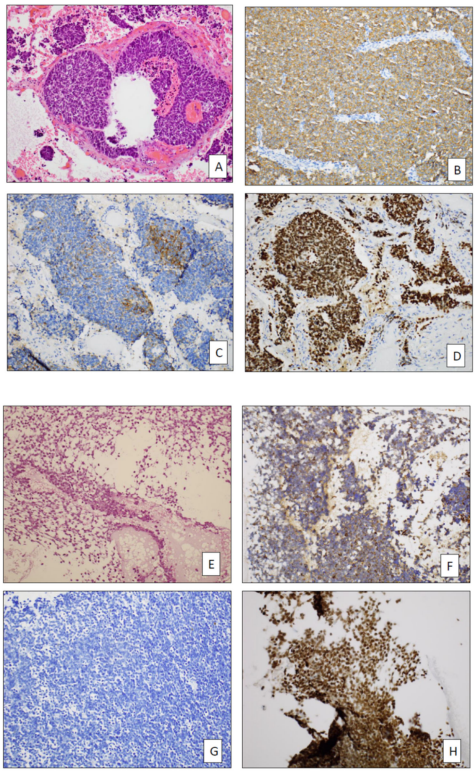

Figure 2. *NUT* lung carcinoma. Tissue (**A**–**D**) and cytological (**E**–**H**) samples from the same patient. (**A**–**D**) Tissue specimen from a lobectomy. (**A**) Proliferation of a poorly differentiated carcinoma (hematoxylin eosin, magnification × 200). (**B**) Expression of cytokeratins (anti-pancytokeratins antibody, immunoperoxidase, magnification × 200). (**C**) A rare NUT tumor expressing the chromogranin (anti-chromogranin antibody, immunoperoxidase, magnification × 200). (**D**) Expression of the protein NUT in the nuclei of carcinoma cells (anti-NUT, clone C52B1, immunoperoxidase, magnification × 200). (**E**–**H**) Bronchial aspirates. (**E**) Numerous poorly differentiated and small and non-cohesive tumor cells (hematoxylin eosin, magnification × 200). (**F**) Weak staining with anti-pancytokeratin antibody (immunoperoxidase, magnification × 200). (**G**) Absence of TTF1 expression in tumor cells (anti-TTF1 antibody, immunoperoxidase, magnification × 200). (**H**) Strong expression of the protein NUT in tumor cell nuclei (anti-NUT, clone C52B1, immunoperoxidase, magnification × 200).

Several clinical trials are ongoing with molecules targeting the bromodomain and extra terminal domain (BET) proteins, which underlines the possible future need to identify these *NUT* carcinomas for personalized treatment, even if these tumors can also be sensitive to ICIs for a long period [287,305–308]. Notably, the current knowledge of BRD4-NUT function has been leveraged for the therapeutic development of first-in-class BET inhibitors, but also other targeted strategies [309–311].

2.4.4. Others Potential Biomarkers of Interest

Other biomarkers are being studied and may join the list of genomic alterations for detection in different genes (such as *STK11*, *KEAP1*, *mitogen-activated protein kinase* (*MEK*), and *phosphatidylinositol 3-kinase catalytic α* (*PI3KCA*)) at diagnosis of advanced-stage NS-NSCLC (Table 1). In particular, some biomarkers may be useful in predicting positive (a high TMB) or negative responses (mutations in *STK11* and *KEAP1*) to treatment with ICIs [312,313]. Certain mutations, such as those in *STK11*, can also open up new avenues of targeted therapies and may be detected with IHC [314,315]. It is noteworthy that the frequency of *STK11* mutations in NS-NSCLC patients seems to be lower (4% in Asians) or higher (25% in African Americans) according to the populations, and comparative to the incidence observed in Caucasians (around 14%) [53,316,317]. To detect genomic alterations in *fibroblast growth factor receptor* (*FGFR*), biomarkers have been developed but their therapeutic application is still preliminary and concerns mostly squamous cell carcinomas of the lung [318–322].

3. What Are the Consequences for Cytology and Liquid Biopsy Practices?

Liquid biopsies and cytological examinations at diagnosis are being used more and more often in daily practice in thoracic oncology. Today, to search for an increasing number of biomarkers predictive of the response to targeted therapies or immunotherapies, the analyses need biological samples from different sources [323,324]. Genomic alteration assessment is feasible on many cytological samples having different preparations [325–327]. Therefore, it is pivotal to perfectly integrate these approaches since in a large number of NSCLC patients the cytology specimen may be the only source of sample available for diagnosis. Mastering and knowing the potential and the limitations of different cytological preparations is mandatory to manage and optimize them for ancillary studies, notably molecular testing, that guide precision medicine. Aside from the use of cytological materials, liquid biopsies can detect a molecular target when a tissue biopsy or a cytological sample cannot be obtained from an inaccessible tumor or in the case of an insufficient number of carcinoma cells [328–330]. However, liquid biopsies at baseline have their limits, in particular in the case of a low amount of circulating DNA from small-sized tumors or in the case of certain metastatic sites (like the brain) that release very little DNA material into the blood [67,331]. Thus, the sensitivity of the different tests for detection of genomic alterations, in particular fusions and amplifications, is globally lower than tests performed with tissue or cells [155]. Moreover, DNA from tissue or circulating in blood can give discordant results [155]. One of the advantages of liquid biopsies compared to tissue biopsies and cytological samples is the possibility of evaluating the tumor heterogeneity, and, thus, of detecting genomic alterations that are sometimes absent from certain tumor sites [332]. Another advantage is certainly the delay in obtaining a result from liquid biopsies, which is shorter compared to tissue biopsies, allowing for adherence to certain international recommendations that require the results be obtained within less than 10 days. Thus, in real life studies, systematic performance of NGS analyses with liquid biopsies show a number of advantages compared to analyses performed with tissue biopsies [333].

While difficult to perform in the routine practice, TMB is a predictive factor in the evaluation of the response to ICIs [334]. Some studies have shown that the analysis of TMB at diagnosis with circulating DNA and with cytological samples can predict the response to ICIs [335–338]. However, analysis of the TMB is not yet performed in most countries and holds a number of limits for use in clinical routine practices [339]. In this regard,

it is essential to perform validation studies evaluating the sensitivity and specificity of the different molecular tests performed with blood and/or cytology compared to tissue specimens before using TMB results obtained with the biological specimens in daily routine.

Altogether, it is of interest to develop an integrative approach that can associate analyses performed with tissues, cytological samples, and those with liquid samples, in particular blood [14,340,341] (Figure 3). Even if NGS approaches from liquid biopsies gain momentum in daily practice they still need to be associated with NGS approaches from nucleic acids extracted from tissue and/or cytological samples. While most of the clinical studies into liquid biopsies are performed with free circulating nucleic acids, a few studies have demonstrated the interest in combining several circulating components for optimal analysis of certain biomarkers [342,343].

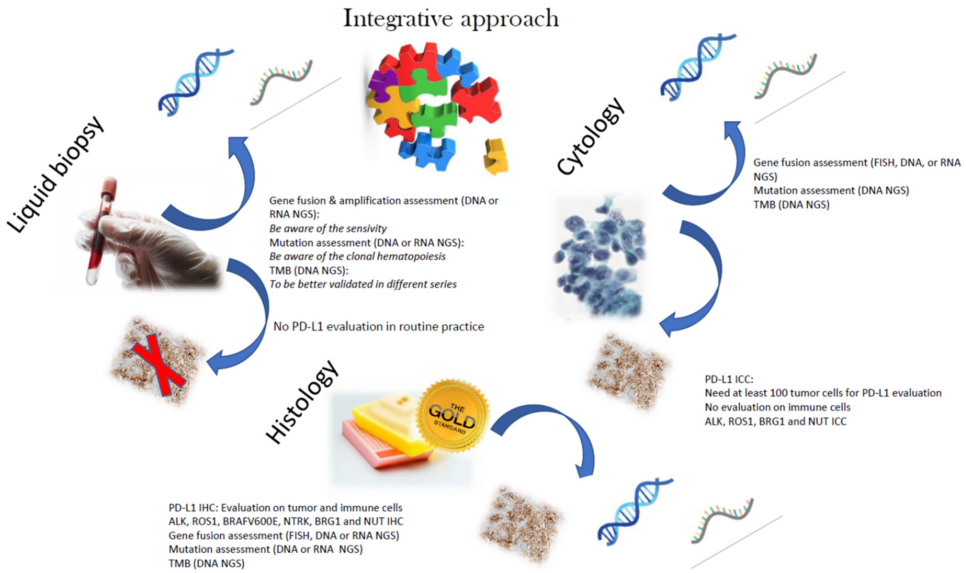

Figure 3. The complementary role of tissue biopsies, cytological specimens, and liquid biopsies for the characterization of presently available and future biomarkers at diagnosis of non-squamous non-small cell lung carcinomas.

4. Conclusions

Improvement in our understanding of the pathophysiological mechanisms of NSCLC and the successive discovery of different predictive biomarkers have significantly modified and made complex both therapeutic and molecular testing algorithms in thoracic oncology. In fact, aside from obtaining the status of *EGFR*, *ALK*, *ROS1*, *BRAF*, and *NTRK* before proceeding with immunotherapy (reserved for patients with more than 50% of tumor cells expressing PD-L1) or immunotherapy associated with chemotherapy (irrespective of the expression of PD-L1 on tumor cells), it is going to be necessary in the short-term to look for genomic alterations in other genes (*RET*, *MET*, *HER2*, *KRAS*, *NRG1*, etc.) at diagnosis. Treating patients with first-line immunotherapy or immunotherapy combined with chemotherapy can be deleterious when patients present with activated mutations in *EGFR* and, depending on the case, rearrangements in *ALK* and *ROS1* [344,345]. For the other genes, the results to date are contradictory and the small number of comparative trials performed at baseline do not allow a consensus to be drawn. However, clinicians need to strongly consider the benefits and risks of starting immunotherapy in symptomatic patients without knowing the complete genomic profile of the tumor, as prescribing suboptimal therapy based on perceived medical urgency may jeopardize outcomes and lead to useless and dangerous toxicity. The choice of the biological specimens of interest for detection of molecular genomic and/or protein biomarkers has evolved, and should integrate tissue biopsies, cytological samples, and/or liquid biopsies to better take care of patients with NS-NSCLC.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: The author thanks Christiane Brahimi-Horn for editing this manuscript, the Conseil Départemental des Alpes Maritimes, the Institut National du Cancer (INCa), the Ligue Départementale de Lutte contre le Cancer des Alpes Maritimes, and the Canceropôle PACA.

Conflicts of Interest: The author declares no conflict of interest.

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