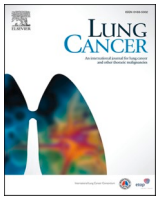
Lung Cancer 181 (2023) 107249

Contents lists available at ScienceDirect

Lung Cancer

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



Review

The significance of co-mutations in *EGFR*-mutated non-small cell lung cancer: Optimizing the efficacy of targeted therapies?

Federica Pezzuto [a,b,*], Véronique Hofman [a], Christophe Bontoux [a], Francesco Fortarezza [b], Francesca Lunardi [b], Fiorella Calabrese [b], Paul Hofman [a,*]

[a] University Côte d'Azur, Laboratory of Clinical and Experimental Pathology, FHU OncoAge, BB-0033-00025, Pasteur Hospital, 30 voie romaine, 06001 Nice, France
[b] Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padova Medical School, Via A. Gabelli 61, 35121 Padova, Italy

ARTICLE INFO

Keywords:
Non-small cell lung cancer
EGFR
Co-mutations
TP53
Targeted therapies
Immune checkpoint inhibitors

ABSTRACT

Non-small cell lung cancer (NSCLC) is the most common cause of cancer death worldwide. In non-squamous NSCLC, the identification of oncogenic drivers and the development of target-specific molecules led to remarkable progress in therapeutic strategies and overall survival over the last decade. Nevertheless, responses are limited by systematically acquired mechanisms of resistance early on after starting a targeted therapy. Moreover, mounting evidence has demonstrated that each oncogenic-driven cluster is actually heterogeneous in terms of molecular features, clinical behaviour, and sensitivity to targeted therapy. In this review, we aimed to examine the prognostic and predictive significance of oncogene-driven co-mutations, focusing mainly on *EGFR* and *TP53*. A narrative review was performed by searching MEDLINE databases for English articles published over the last decade (from January 2012 until November 2022). The bibliographies of key references were manually reviewed to select those eligible for the topic. The genetic landscape of *EGFR*-mutated NSCLC is more complicated than what is known so far. In particular, the occurrence of *TP53* co-mutations stratify patients carrying *EGFR* mutations in terms of treatment response. The study provides a deeper understanding of the mechanisms underlying the variability of the genetic landscape of *EGFR*-mutated NSCLC and summarizes notably the clinical importance of *TP53* co-mutations for an open avenue to more properly addressing the clinical decision-making in the near future.

1. Introduction

Lung cancer represents the most common cause of cancer death with 1.80 million deaths in 2020 [1]. Lung cancer is divided into two categories, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), accounting for 85% and 15% of cases, respectively, which differ for biology, treatment, and prognosis. In NSCLC, non-squamous (NS) histology is the most common histotype, detected in almost 80% of diagnoses [1,2]. In the latter subgroup, the therapeutic strategies have made notable progress in the last decade, as result of the new findings in the field of study of molecular alterations of this neoplasia. Indeed, numerous somatic mutations and genomic rearrangements have been found in high rates. The acquired genetic alterations of driver genes have been associated with tumour growth and progression as well as the development of targeted therapies which many patients can benefit from. The most frequent mutations in NSCLC in Caucasian population are in the driver genes a) kirsten rat sarcoma-*KRAS* (29%), b) epidermal growth factor receptor-*EGFR* (19%), c) B-Raf proto-oncogene-*BRAF* (5%), d) anaplastic lymphoma kinase-*ALK* (3%), e) *MET* proto-oncogene-*MET* (3%), f) human epidermal growth factor receptor 2-*HER2* (3%), g) ret proto-oncogene-*RET* (1%), h) *ROS* proto-oncogene 1-*ROS1* (1%), i) neurotrophic tyrosine receptor kinase -*NTRK*, neuregulin 1 -*NRG1* (<1%), and, j) other genes (9%) [3,4].

However, the picture of this genomic landscape is far from complete.

Abbreviations: ALK, anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogzzene; CTNNB1, catenin Beta 1; CDK, cyclin D-dependent kinases; EGF, epidermal growth factor receptor; E2F1, E2F transcription factor 1; Foxp3, forkhead box P3; GSK-3β, glycogen synthase kinase-3 beta; HER2, human epidermal growth factor receptor 2; KEAP1, Kelch-like ECH associated protein 1; KRAS, kirsten rat sarcoma; LUAD, lung adenocarcinoma; MET, MET proto-oncogene; MDM2, mouse double minute 2 homolog; NRG1, neuregulin 1; NTRK, neurotrophic tyrosine receptor kinase; NGS, next generation sequencing; NSCLC, non-small cell lung cancer; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RET, ret proto-oncogene; ROS1, ROS proto-oncogene 1; SCLC, small cell lung cancer; TMB, tumou mutation burden; SCC, squamous cell carcinoma; TILs, tumour-infiltrating lymphocytes; TME, tumor microenvironment; PD-L1, programmed death-ligand 1.

* Corresponding authors.
E-mail addresses: federica.pezzuto@unipd.it (F. Pezzuto), hofman.p@chu-nice.fr (P. Hofman).

https://doi.org/10.1016/j.lungcan.2023.107249
Received 27 February 2023; Received in revised form 3 May 2023; Accepted 11 May 2023
Available online 18 May 2023

About 27% of the mutations remains unknown [3]. Moreover, the spectrum of mutations has been enriched with the advent of molecular studies using increasingly sophisticated techniques, such as large panels of next generation sequencing (NGS). While mounting evidence has shown that each oncogenic-driven cluster is heterogeneous in terms of molecular features, clinical behaviour, and sensitivity to targeted therapy is with an unmet need of ameliorating our understanding of the mechanisms underlying this variability [5].

In this review, we aimed to examine the significance of oncogene-driven co-mutations in patients' outcomes, focusing on *EGFR* whose molecular alterations are routinely required in the workflow of NS NSCLC.

A narrative review was performed by searching MEDLINE databases for English articles published until November 2022 by using the key terms: co-mutations, *EGFR*, NSCLC, tyrosine kinase inhibitors (TKI), tumour microenvironment (TME), and immunotherapy. The bibliographies of key references were manually reviewed to determine eligibility for the topic of this review.

2. Co-mutations in *EGFR*-mutated lung adenocarcinoma (LUAD)

The occurrence of co-mutations in NSCLC have potentially more impact than single specific mutations in oncogenic drivers for the determination of the tumour heterogeneity. Not all mutations have the same meaning. While "driven" mutations affect standard genetic drivers strictly related to cancer, other "passenger" mutations can lead to variants without any impact or with small but measurable impact on cancer [6]. Even if rarely, passenger mutations can also be slightly protective against cancer.

The distinction between passenger and driver mutations, such as in *EGFR*, is not absolute because a mutation can have different effects in different tumours. This statement is generally supported by current scientific knowledge [7–10], as mutations in a gene like *EGFR* can have varying effects on different types of solid tumours or even within different regions of the same tumour. While certain *EGFR* mutations may be considered as "driver mutations" in one tumour, they may not have the same effect in another tumour type and may even be considered as "passenger mutations." This suggests that the classification of a mutation as a "driver" or "passenger" mutation may not always be straightforward and may depend on the context in which this mutation occurs. Indeed, the development of lung cancer is a complex process that involves a combination of genetic and environmental factors, and that the effects of mutations in genes like *EGFR* may depend on the context in which they occur [5,11]. Mutations may interact with other genetic aberrations, as well as with external factors like mutagens or radiation, to create diverse patterns that contribute to the development of lung cancer [12–14]. Additionally, epigenetic changes, which can affect gene expression without altering the underlying DNA sequence, may also play a role in shaping the cancer phenotype [15]. Epigenetic changes are alterations in gene expression that occur without any changes in the underlying DNA sequence. These changes can be heritable, meaning that they can be passed on from one generation to the next, and they can also be reversible, meaning that they can be modified by environmental factors [15]. In cancer, epigenetic changes can affect the expression of genes that regulate cell growth, differentiation, and death. For example, DNA methylation, histone modifications, and microRNA expression can all influence the expression of genes that are involved in cancer development and progression [15]. Abnormal epigenetic changes can lead to the activation of oncogenes, which promote cell proliferation, or the silencing of tumour suppressor genes, which normally prevent cell growth and division. These changes can contribute to the development of a cancer phenotype, which includes features such as uncontrolled cell growth, invasion into surrounding tissues, and the ability to metastasize to distant sites [15]. Understanding how epigenetic changes contribute to cancer development and progression is an important area of research, as it may lead to the development of new therapeutic approaches for the treatment of cancer [15].

Epigenetic changes play a significant role in shaping the cancer phenotype, including LUAD. Alterations in DNA methylation, histone modifications, and microRNA expression can affect gene expression without altering the underlying DNA sequence. However, it's important to note that LUAD is a highly heterogeneous disease, and different patterns of growth can lead to intratumor heterogeneity [16,17]. This aspect is poorly investigated in the literature, which often considers LUAD as a unique entity. Future studies should account for the potential impact of intratumor heterogeneity on epigenetic changes in LUAD and explore its implications for diagnosis, prognosis, and treatment. Understanding the complex interplay between epigenetic changes and intratumor heterogeneity will be crucial for developing personalized and effective therapies for LUAD patients [18].

Another consideration regarding the contribution of a mutation is about how much mutation can be detected in tumour tissue. A first point is the measure of the proportion of DNA molecules in the original specimen carrying the variant, identified as the variant allele frequency [19]. A second point is the topic of clonality. In general, clonality is the overrepresentation of a single gene product in a polyclonal background. Sometimes, the variant can be represented only in a group of cells and only in a part of the tumour, as a subclone. These variants can develop from the accumulation of mutations during tumour progression under the pressure of uncontrolled growth and they can as well derive from the selection of a clone under the pressure of a therapy [20]. That is why the most correct timing to interpret and understand the functional significance of co-mutations is probably at the beginning of tumour development, in early/locally advanced stages when there is a naïve condition of heterogeneity due the tumour itself.

EGFR-mutated LUAD is a category largely investigated by further molecular analyses, where the occurrence of co-mutations has been known for long time. Some mutations appear as recurrent in this group, with special reference to tumour protein p53-*TP53*, in at least half of the cases, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha-*PIK3CA*, retinoblastoma-*Rb1* or Catenin Beta 1-*CTNNB1* [20]. These co-mutations are independent from the initiating *EGFR* mutation, showing a superimposable prevalence in each subgroup [21], while their number tend to increase after treatment. Interestingly, they show different distribution among tumour stages. Indeed, *TP53* and *Rb1* mutations are already detected in early-stage NSCLC. In contrast, *PIK3CA* and *CTNNB1* mutations are more frequent in advanced stages, suggesting that they appear in a later phase of the carcinogenesis, probably as an additional event to the existing *EGFR* mutation, being prevalently involved in malignant progression and metastases [5,22]. Finally, although rarer, other co-mutations may occur, such as NK2 homeobox 1-*NKX2–1*, Cyclin D-dependent kinases *(CDK)4*, *CDK6*, *CNE1*, and Kelch-like ECH associated protein 1-*KEAP1* co-mutation [20]. Also based on recent acquisition in LUAD, the latter merits further considerations.

3. *TP53* co-mutation

3.1. Structure and function of the protein

The *TP53* gene is located on the short arm of chromosome 17. The protein acts when a DNA damage is detected, blocking the G1/S transition of the cell cycle, activating the DNA repair protein or, when it is irrevocable, initiating apoptosis [23].

TP53 is composed of seven domains. Most deactivating mutations occur in the central DNA-binding core domain preventing the association of the protein to the co-factor LIM Domain Only 3-LMO3 and thus the binding to the DNA sequences and the consequent transcriptional activation of some genes (recessive loss of function mutations) [24–26]. Mutant p53 protein also exhibits a dominant negative activity over the wild-type p53 protein by inhibiting its ability to bind the promoter [27].

The mechanisms for p53 activity are complex. Both intrinsic and extrinsic stimuli can activate *TP53*. Briefly, the DNA damage is detected

by proteins that with enzyme activities that in turn activate post-translational modifications resulting in phosphorylation, acetylation, methylation, ubiquitination or SUMOylation of the p53 protein. Independently of the cause, as an oncogenic activation, the ARF protein interacts with Mouse double minute 2 homolog-MDM2 retaining it into the nucleolus. This blocks the proteasomal degradation of p53 that initiates its pathway [28].

Additional mechanisms can also result in the inhibition or in the downregulation of *TP53* in cancer cells. These mechanisms notably include the downregulation of the long noncoding RNA P53RRA,[29], which is associated with poor survival in some cancers, and the inactivation of *TP53* by lymphoid-specific helicase [30]. These findings underline the complexity of *p53* regulation in cancer cells and the need for a more comprehensive understanding of the molecular mechanisms involved. By identifying and targeting these mechanisms, researchers may be able in the near future to develop more effective treatments for cancers in which p53 is dysregulated or inhibited.

When p53 is altered, the most important downstream pathway is mediated by p21 protein whose function is to inhibit cyclin-dependent kinase 2-CDK2, functionally responsible for the activation of Rb that in turn derepressed the E2F transcription factor 1-E2F1 activity, thus blocking the expression of genes related to G1/S transition. Most genes regulated by p53 are involved in the secretion of cytochrome *c* into the cytoplasm from the mitochondria, thus initiating the intrinsic pathway of apoptosis. When *TP53* is altered, this cascade is inactive. Several other signalling pathways are strictly related to p53 function in a complex network of interactions [28].

3.2. TP53 polymorphism and cancer susceptibility

In biology, alternative phenotypes are admitted, and gene polymorphism is frequent. The majority of polymorphisms are silent, meaning they do not alter the function or expression of a gene. The substitution of an arginine for a proline at codon 72 of exon 4 is a common polymorphism in *TP53*. Its significance in terms of cancer susceptibility has been investigated but results are still debated. Some studies and metanalyses showed that a certain increase in cancer risk was evident in association with this polymorphism in several types of tumours [31–34]. In contrast, other authors have not found any correlation between the abovementioned polymorphism and cancer susceptibility [35–38]. Therefore, the question remains open until now.

3.3. TP53 mutations

TP53 mutation have been divided into two categories: disruptive (non-conservative) and nondisruptive (conservative). The first category includes mutations involving the DBD and stop codon in any region; the second one is composed of mutations outside the DBD. The two types of mutations determine different effects on p53 function. If in the first case, p53 loses its function, either completely or only partially, in the second occurrence p53 can retain some functions of the non-mutated protein form or, sometimes, can gain new functions [39–41].

In NSCLC, at least 80% of cases are represented by missense mutations, mostly affecting the exon 4–8 in the DBD. *TP53* mutations show a distribution among the different histotypes. The most affected one is squamous cell carcinoma [42]. In LUAD, suppressor gene abnormalities (including *TP53*) have been commonly found. *TP53* somatic alterations have been reported in up to 46% of cases, mainly in oncogene-negative tumours [18]. The prevalence of mutations is also correlated with the smoking history. Moreover, prognosis is also influenced by *TP53* mutations. Indeed, in non-smoker patients, the detection of *TP53* mutation is an independent negative prognostic factor [42].

3.4. Significance of TP53 co-mutations in EGFR-mutated LUAD: Lights and shadows

Knowledge about the coexistence of *TP53* and *EGFR* mutations in LUAD has increased in the last five years (Fig. 1). The prevalence of this association ranges from 22.4% to 72.5% [41,43–49] with high incidence also in early stages [50]. The different range of prevalence is quite surprising. The main explanation is related to the heterogeneity of the more or less sophisticated methodologies and techniques used for molecular screening, with more or less large panels that could also have caused the loss of important but misrecognized mutations as relevant epigenetic events [51]. For instance, although amplicon-based sequencing is largely used, having the great advantage of a simplified workflow and small amounts of DNA required for diagnosis, hybridization-based strategies are less likely to miss mutations [52]. As such, for *TP53* some exons may not be covered and therefore the mutation not detected.

Despite the fact that making a comparison between incidences, prevalence, and clinical significance of *TP53* co-mutation has been difficult so far, in terms of clinical significance of *TP53* co-mutations, its impact has been demonstrated on overall survival [41,49,53–64], on progression free survival [47,65–68,68–79], and on both type of survival [48,48,56,80–84] with variable results (Table 1).

It has been consistently demonstrated that *TP53* mutations negatively affect the response to 1st line TKI treatment with first [84] and second generation TKI [57]. Recently, Roper et al. [83] showed that *TP53* co-mutations may affect PFS and OS in this population, thus suggesting the need of new therapeutic strategies for this subgroup [83]. Similar results have also been reported by Vokes et al. [85] who observed a nonsignificant trend toward decreased PFS on later-line of Osimertinib. While the impact of *TP53* mutations seems to be independent from the generation of EGFR-TKI, data on the predictive impact has not been clarified yet for the 3rd generation TKI Osimertinib when used in frontline setting, as recommended by the guidelines following the results of the FLAURA trial [86]. Le et al. have included these patients in their study, confirming the worse outcome of the *TP53* co-mutation in patients receiving 1st line EGFR-TKI monotherapy [87]. In this study, Osimertinib was the most common TKI administered. However, the limited follow up and the potential confounding bias may limit the strength of these results and require validation in further studies.

3.5. TP53 specific exon alterations

The spectrum of *TP53* mutations is wide in relation to the exon affected by genetic events. Only a few studies have considered different *TP53* types of mutations.

In 2017, Canale et al. demonstrated that *TP53* was associated with a shorter PFS and OS, mainly when affecting exon 8 and in association with *EGFR* exon 19 deletion in a first line setting [84]. The same group, some years later, also showed that the same negative prognostic impact in patients treated with second and third generation TKI after resistance acquisition [57]. These results were further supported by Roper et al. [83] who found a statistically significant PFS and OS when using *TP53* exon 8 to categorize co-mutated patients. (Table 2). If *TP53* exon 8 alterations are expected to be more frequently detected, [48,56,57,70,77,84,88], pieces of evidence suggest that also exon 4, 5, 6 and exon 7 may be altered with a negative impact on survival [56,77,81,82,89]. (Table 2) The most important clinical aspect that merits further consideration in the future is the significance of different *TP53* co-mutations in terms of benefit for TKI monotherapy or combination with chemotherapy that seems to be more effective in this setting. However, what should be kept in mind is that all these studies are retrospective, thus affected by several biases. Moreover, very often the patients undergoing monotherapy are also those with more comorbidities that could have driven the more unfavourable prognosis. In Fig. 2

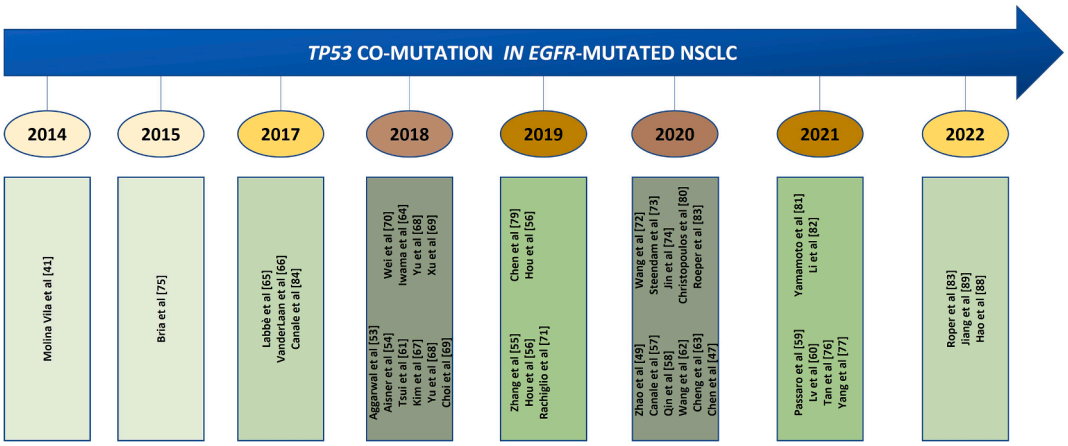


Fig. 1. Timeline of research studies on *TP53* co-mutation in *EGFR*-mutated NSCLC. The timeline shows a significant increase in the number of reports in the literature from 2014 to 2022.

Table 1
Clinical significance of *TP53* co-mutations.

AUTHOR	YEAR	N° OF CASES	STAGE	CLINICAL IMPACT
Molina Vila et al. [41]	2014	318	IIIB-IV	OS
Bria et al. [75]	2015	17	ns	PFS
Labbè et al. [65]	2017	105	all	PFS
VanderLaan et al. [66]	2017	171	IV-recurr	PFS
Canale et al. [84]	2017	136	adv	OS and PFS
Aggarwal et al. [53]	2018	131	IV	OS
Aisner et al. [54]	2018	1367	IV-recurr	OS
Tsui et al. [61]	2018	50	IV	OS
Kim et al. [67]	2018	75	adv	PFS
Yu et al. [68]	2018	374	metast	PFS
Choi et al. [69]	2018	60	adv	PFS
Wei et al. [70]	2018	41	progr	PFS
Iwama et al. [64]	2018	25	IIIB-IV-recurr	PFS
Xu et al. [78]	2018	28	III-IV	PFS
Zhang et al. [55]	2019	*meta*-analysis 2979	all	OS
Rachiglio et al. [71]	2019	133	IIIB-IV	PFS
Chen et al. [79]	2019	423	III-IV	PFS
Hou et al. [56]	2019	163	III-IV	OS and PFS
Zhao et al. [49]	2020	675	all	OS
Canale et al. [57]	2020	136	adv	OS
Qin et al. [58]	2020	*meta*-analysis 1342	IIIB-IV-recurr	OS
Wang et al. [62]	2020	476	all	OS
Cheng et al. [63]	2020	179	adv	OS
Chen et al. [47]	2020	36	I,III,IV	PFS
Wang et al. [72]	2020	240	ns	PFS
Steendam et al. [73]	2020	41	ns	PFS
Jin et al. [74]	2020	54	ns	PFS
Christopoulos et al. [80]	2020	400	ns	OS and PFS
Roeper et al. [48]	2020	75	IV	OS and PFS
Passaro et al. [59]	2021	284	adv	OS
Lv et al. [60]	2021	233	adv	OS
Tan et al. [76]	2021	180	adv	PFS
Yang et al. [77]	2021	137	adv	PFS
Yamamoto et al. [81]	2021	154	IIIB-IV	OS and PFS
Li et al. [82]	2021	195	adv	OS and PFS
Roper et al. [83]	2022	77	IV	OS and PFS
Jiang et al. [89]	2022	210	I-IV	OS
Hao et al. [88]	2022	139	adv	OS

Abbreviations: ns: not specified; adv: advanced; PFS: progression free survival; OS: overall survival; recurr: recurrence.

Table 2
Summary of the studies considering *TP53* types of mutations distinctly.

AUTHOR	YEAR	N° OF CASES	*TP53* MUTATION	STAGE	CLINICAL IMPACT
Canale et al. [84]	2017	136	exon 8	adv	OS + PFS
Wei et al. [70]	2018	41	exon 6 and 8	progr	PFS
Hou et al. [56]	2019	163	exon 6 and 7	III-IV	OS + PFS
Canale et al. [57]	2020	136	exon 8	adv	OS
Roeper et al. [48]	2020	75	exon 8	IV	OS + PFS
Yamamoto et al. [81]	2020	152	exon 5, 6, and 7	IIIB-IV-recurr	OS + PFS
Yang et al. [77]	2021	137	exon 4 and 6	adv	PFS
Li et al. [82]	2021	195	exon 4 and 7	adv	OS + PFS

Abbreviations: adv: advanced; recurr: recurrences; progr: progression; PFS: progression free survival; OS: overall survival.

an emblematic case of an *EGFR*-mutated LUAD and a *TP53* co-mutation is reported.

3.6. *TP53* co-mutations and type of *EGFR* mutations

TP53 co-mutations are reported to have different clinical impact according to the different types of *EGFR* mutations (Table 3). Patients with exon19 deletion of *EGFR* are usually more sensitive to TKI than other *EGFR*-mutated patients. If *TP53* worsens the *EGFR* TKI response, it is not surprising that most evidence highlight the negative effect of *TP53* mutation in this group [66,69,71,80,84]. However, in some studies, the mutation of exon 21 L858R seems more affected by *TP53* co-mutation in comparison with exon 19 deletion [81,90]. *TP53* mutations in case of *EGFR* T790M resistance should especially be mentioned because *TP53* has also resulted to be a negative prognostic, too [74,83,91]. These data further highlight the need to find alternative therapeutic strategies in case of resistance.

We also need to be aware of the association of *TP53* with uncommon *EGFR* mutations (in particular *EGFR* exon 20 insertions) since new efficient drugs have been (amivantanab and mobocertinib) [92] FDA and EMA (amivantanab) or FDA (mobocertinib) approved or might be approved in the future (CLN-081) [93]. Due to limited availability of data concerning this rare alteration, standard-of-care is unclear. Moreover, this group is heterogeneous in terms of insertion variant, incidence and type of co-mutations, and TME features [94], thus making it difficult to understand what factors and mechanisms are involved in modulating

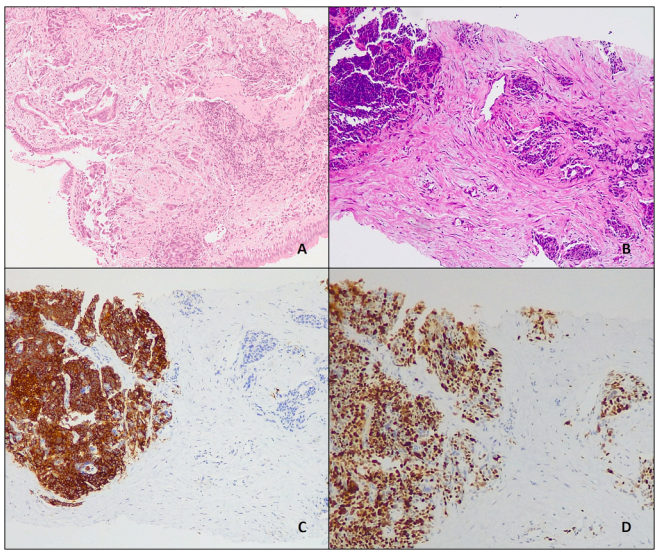


Fig. 2. Index case of a *TP53* co-mutation in an *EGFR*-mutated lung adenocarcinoma. The patient was a 59-year-old non-smoker female. In April 2020 a diagnosis of lung adenocarcinoma was performed on transbronchial biopsy: A) haematoxylin and eosin, original magnification × 100. Molecular analysis showed exon 19 deletion of *EGFR*. III-line TKI therapy was implemented. Eighteen months later, the patient presented disease progression with pleural involvement. A core biopsy was performed showing solid nests of poorly differentiated neoplastic cells, immunoreactive for neuroendocrine markers and with high proliferative index (B: haematoxylin and eosin, original magnification × 100; C: synaptophysin, original magnification x100; D: Ki67, original magnification x200). The diagnosis on the recurrence was consistent with a small cell lung adenocarcinoma. A liquid biopsy showed exon 19 deletion of *EGFR* and a missense mutation of *TP53* in exon 7, c.742C > T, p.Arg248Trp, with a variant allele frequency of 0.96%. The patient died one month after the diagnosis.

Table 3
Summary of the studies considering *TP53* co-mutations in different types of *EGFR* mutations.

AUTHOR	YEAR	N° OF CASES	*TP53* MUT SPEC.	STAGE	*EGFR* MUTATIONS
Canale et al.[84]	2017	136	yes	adv	ex19
VanderLaan et al. [66]	2017	171	ns	IV-recurr	ex19
Lee et al. [91]	2017	19	ns	IIIA-IIIB-IV	T790M
Choi et al. [69]	2018	60	ns	adv	ex19
Rachiglio et al. [71]	2019	137	ns	IIIB-IV	ex19
Zeng et al. [90]	2020	491	ns	all	L858R
Christopoulos et al. [80]	2020	400	ns	ns	ex19
Jin et al. [74]	2020	54	ns	ns	T790M
Yamasoto et al. [81]	2021	154	yes	IIIB-IV	L858R
Roeper et al. [83]	2022	77	yes	IV	T790M

Abbreviations: adv: advanced; recurr: recurrences; PFS: progression free survival; OS: overall survival, ns: not specified.

the response to drugs. *EGFR* ex20ins mutated NSCLCs were also demonstrated to be less sensitive to immune check point inhibitors (ICIs) [95] with shorter median time to next therapy after the first ICI treatment, as previously reported in patients with exon 19 deletion and L858R *EGFR*-mutated NSCLC [96–100]. Another recent study, Christopoulos et al [101] systematically analysed 118 patients harbouring *EGFR* ex20ins for type of mutations and different treatments. Chemotherapy treatment was associated with a significantly better PFS than TKI, while immunotherapy was ineffective. Interestingly, *TP53* co-mutation was associated with worse survival, independently of treatments and drugs, thus reinforcing the need of a large and deep molecular characterization so as to identify further routine practices.

3.7. TP53 and tumour stage

Another interesting aspect of these studies that focused on *TP53* is that almost all included patients with NSCLC of all clinical stages or, more frequently only advanced tumour. Only a few reports addressed early stages solely [50,102]. The main explanation is related to the limitation of molecular profiling in advanced or inoperable stages before the ADAURA trial. As mentioned above, in these stages a high percentage of *TP53-EGFR* mutations has been described among the *EGFR* mutated population of patients, up to 72% [50], as well as a certain role in prognosis of patients, mainly for DFS and PFS [50,102]. However, it should be recognized that an intrinsic bias of selection of the study populations and the limited information about follow up may limit the strength of this evidence.

3.8. TP53 and squamous cell carcinoma (SCC)

Most studies concerning the role of *TP53* mutations in NSCLC focused on NS NSCLC. However, given the association between *TP53* mutations and smoking habits [103], its occurrence is also expected in SCC. Concerning *EGFR*-mutated SCC, it seems to be more similar to *EGFR*-mutated LUAD than *EGFR* wild type SCC, except for a lower PFS and the frequency of some co-mutations [104]. Notably, there was a similar mutation frequency for *TP53* in comparison with *EGFR*-mutated LUAD and, also in this group, this mutation seems to be associated with reduced TKI efficacy [104].

3.9. TP53 co-mutations and TME in EGFR-mutated NSCLC

In *EGFR*-mutated LUAD, the TME appears to be “quiescent” (i.e., most tumours are “cold tumours”) due to multiple causes. *EGFR* mutation is associated with reduced density and function of CD8 + tumour-infiltrating lymphocytes (TILs), thus reducing the immune-mediated tumour-killing effect. *EGFR*-mutated NSCLC is associated with upregulation of CD73. It is an enzyme that in humans is encoded by the *NT5E* gene and serves to convert adenosine monophosphate-(AMP) to adenosine. When upregulated, the excess of adenosine further promotes Treg and myeloid-derived suppressor cells, thus hindering the immune response. *EGFR* mutation also up-regulates amphiregulin which is associated with activation of the pathway EGFR/ glycogen synthase kinase-3 beta-GSK-3β/ forkhead box P3-Foxp3, promoting Treg functions [105].

Another peculiarity in the TME in *EGFR*-mutated NSCLC is related to the tumou mutational burden (TMB), defined as the total number of somatic/acquired mutations per coding area of a tumour genome (Mut/Mb). In case of exonic mutations, on tumour surface novel protein epitopes show up that increase immunogenicity and trigger an immune response. TMB is highly variable in various cancers and appears to be associated with certain factors such as smoking, which increases it. Therefore, it is understandable that it is low in *EGFR*-mutated NSCLC who are usually non-smokers it is low [105].

Another key player in TME is the programmed death-ligand 1 (PD-L1). Preclinical studies demonstrated that PD-L1 was highly expressed in *EGFR*-mutated LUAD [106,107]. However, the clinical evidence for PD-L1 in *EGFR*-mutated tumours showed that these patients developed hyperprogression after treatment with ICIs and a high incidence of severe adverse events. The discrepancies between preclinical and clinical findings indicate a complex relationship among *EGFR* mutations, the TME, and therapeutic response from immunotherapy. In contrast, in *KRAS*-mutated NSCLC the behaviour of PD-L1 is the opposite and it is

influenced negatively by the presence of the co-mutation [108]. For instance, the co-occurrence of *KRAS/STK11* is quite common (detected in about a quarter of cases) and associated with lower levels of TIL and PD-L1 levels [109]. Similar findings have also been demonstrated for *KRAS/KEAP1*, leading to resistance or refractory to immunotherapy [110]. In contrast, *KRAS/TP53* co-mutations are associated with an inflammatory response of the *KRAS/TP53* immune profile and thus with an improved response to ICI [111]. This is also true for the *KEAP1/TP53* double mutant whose behaviour was superimposable to the latter [112].

Based on this data, Choong et al identified three clusters of somatic mutations in 88 untreated LUAD, harbouring *EGFR, EGFR* and *TP53*, and multiple gene-mutations, respectively. By performing transcriptomic and proteomic analysis, they found a higher PD-L1 protein expression in the *EGFR* and *TP53* co-mutation subtype than in the *EGFR* mutation subtype [113]. More recently, Jin et al. [108] studied a large population of 819 patients for PD-L1 and molecular analyses by a 68 gene panel. They found that PD-L1 values changed in combination to driver mutation, being higher in *EGFR* wt, *KRAS* and *MET*-mutated, and *ALK, ROS1*, and *NTRK* translocated. Moreover, PD-L1 increased when associated with *TP53* and *Rb1* co-mutation. Finally, when these co-mutations were associated with *EGFR* mutations PD-L1 expression was high if compared to *EGFR*-mutated alone. This was clinically relevant because when PD-L1 was high patients had higher risk of recurrence and patients with negative PD-L1 expression harbouring suppressor gene mutation had significantly poorer prognosis.

In the context of the importance of the genetic profile in the determination of TME, the immune characteristics of *EGFR*-mutated NSCLC appear heterogeneous. Indeed, although the overall benefits of ICI in this category are low, some patients can show a good response. The main explanation for this discrepancy lies in the diversity of the TME in distinct *EGFR* mutations. Not all *EGFR*-mutated tumours are "cold", as described above. *EGFR* L858R mutated tumours show higher TMB levels, CD8 + infiltrate, and PD-L1 expression in comparison with *EGFR* exon 19 deletions. Similar data are also described in uncommon *EGFR* mutations (e.g., G719X) [96]. The biology underlying this diversity needs to be clarified in the near future.

In terms of genetic and immunologic cooperation, an interesting field of interest on the significance of *TP53* co-mutations and the immunologic status of *EGFR* mutated LUAD is that related to exon 20 insertions. These tumours are still a therapeutic challenge, being intrinsically resistant to the action of conventional TKIs. The modulation of the therapeutic effects is supposed to be dependent on the heterogeneity of this group, especially regarding the insertion variant, the action of co-mutations, and the features of TME [114]. In a recent article, Christopoulos et al. evaluated the radiological response of a large numbers of LUAD arising in exon 20 insertion and treated with different chemotherapy, immunotherapy, and chemoimmunotherapy schemes. Interestingly, the detection of a *TP53* mutation and a low tumour CD8/Th1-cell ratio was independently associated with a worse prognosis [101], thus further supporting the clinical relevance of assessing both co-mutations and TME in these tumours.

4. Targeting *TP53* co-mutations

Several attempts have been made at targeting *TP53* mutations [115]. Preventing the degradation of mutated p53 is probably the most intuitive approach. MDM2 is the major negative regulator of p53, preventing p53 from entering the nucleus. Thus, its inhibition may promote p53 proteasomal degradation. However, this is a strategy that has a rational exclusively in cases where p53 is partially maintained [28]. When p53 is completely lost, two other approaches may be attempted: on the one hand, suppressing the function of the mutated p53, on the other hand promoting its degradation. Another possibility is possibly to restore the function of the mutated protein, for example by changing the protein structure with temperature or by creating an alternative DNA binding site [116]. Several compounds have been developed, with a modest clinical response and high number of adverse events [116]. In a few cases they are administered in phase I and II clinical trials, showing promising results in myelodysplastic syndromes and AML [116].

More recently, Song et al. [117] examined 800 common *TP53* mutations to determine their susceptibility to a generic rescue compound, arsenic trioxide (ATO), based on their transactivation activity, cell growth inhibition, and tumour-suppressive activities in mice. A total of 390 p53 mutants were rescued to varying degrees and classified as type 1, type 2a, and type 2b mutations based on the degree of rescue. The authors found that ATO preferentially inhibited the growth of tumours with type 1 and type 2a mutations. The study has provided a resource of the draggability of numerous *TP53* mutations and has proposed a p53-targeting strategy based on individual mutant alleles rather than mutation type.

The time for this scenario is not yet ripe. The main limitation is that, since p53 is involved in a series of fundamental mechanisms for cellular homeostasis, when one interferes with it, all other connected pathways are modified, even in healthy cells. This may be overcome through nanomedicine-based therapy which can significantly enhance drug efficacy while minimizing adverse effects. Finally, *TP53* mutations are complex and with different effects. The determination of a mutant p53 structure is mandatory, as multiple p53 mutations necessitate the use of multiple agents directed against mutant p53, let alone the specific and effective functions of the mutant p53 reactivator/inhibitor. A further possibility is to work around the p53 pathway, targeting an alternative pathway to p53 such that the combination of the two effects is lethal for the mutated cell. It is not a distant reality since PARP inhibitors already used in clinical settings exploit this mechanism of synthetic lethality [116].

5. Other co-mutations in *EGFR*-mutated LUAD

Although *TP53* mutations are the most frequent co-mutations occurring in *EGFR*-mutated LUAD, other genes are also involved, with different prevalence and significance.

5.1. *CTNNB1* co-mutations

CTNNB1 is the gene located on chromosome 3, encoding for β-catenin which plays a pivotal role in cell adhesion and intercellular communication. Its aberrant activation contributes to carcinogenesis and tumour progression. It is not surprisingly that this alteration is more frequently detected in advanced stage, being involved in processes that start late in the tumour progression and dissemination [20,118].

The clinical significance of *CTNNB1* co-mutation in *EGFR*-mutated LUAD is mainly based on experimental studies that highlighted an increased invasive potential of NSCLC cells in vitro [20]. However, in a mouse model a function in promoting tumour initiation was also suggested by the evidence that genetic deletion of *CTNNB1* reduced tumour burden [20]. Concerning the association with *EGFR* mutations, *CTNNB1* was found to be more frequent in *EGFR* T790M after TKI, suggesting an enhanced genetic interaction in this setting [20]. The strict interaction with *EGFR* was also demonstrated by the direct action of *EGFR* mutated LUAD in stabilize b-catenin allowing its nuclear accumulation through the phosphorylation of the same β -catenin [20].

Although few, there is some evidence about the morphological "phenotype" of tumours harbouring *EGFR* and *CTNNB1* mutation. De Montpreville et al showed that in almost half the cases this was present in combination with an *EGFR* mutation. [106]. Morphologically, such tumours were more frequently papillary and strongly immunoreactive for TTF1 [119]. The evaluation of β-catenin in immunohistochemistry was extremely heterogenous and in only a few cases gene mutation was detected also through molecular analyses, thus limiting the use of this method in a routine approach.

5.2. Rb1 co-mutations

Rb1 is located on chromosome 13 and is the tumour suppressor gene that was first discovered to act as a key negative regulator of the G1/S transition in the cell cycle [120]. The most important fact that must be underlined is that the *Rb1* mutation is usually detected together with the *TP53,* mutually reinforcing their action in cell cycle deregulation [121]. This combination has been called into question in the complex mechanism of morphological-molecular transformation of LUAD into SCLC. Indeed, they are considered the pivotal mutations in SCLC, as emerged from genome sequencing studies. The triple mutated *EGFR-Rb1-TP53* was even a high-risk phenotype, in terms of phenotypical switch, such as to justify the upfront use of TKI and platinum/etoposide-based chemotherapy in new clinical trials (NCT03567642). However, the matter is much more complicated than that and several considerations about *Rb1* loss should be highlighted. The most important one is that these mutations are necessary but not sufficient conditions to induce transformation. Several pathways, transcriptional and epigenetic events influence genetic modifications such as to make NSCLC cells more like SCLC ones.

5.3. PIK3CA co-mutations

PIK3CA is a protein encoded by a gene located on chromosome 3 that acts as the catalytic subunit alfa of the enzyme PI3K that transduce intracellular signals associated with regulation of cell growth and proliferation [122]. Two main hotspots for activating mutations are recognized for *PIK3CA* [123]. *PIK3CA* mutation has been found in association with *EGFR* mutation independently from the category of this latter. The detection of these co-mutations has been linked to relevant clinical aspects, being associated with higher frequency of lymph node metastases, higher drug resistance and shorter survival after EGFR-TKIs [124].

5.4. KEAP1 co-mutations

KEAP1 is the protein encoded by the homonymous gene of the chromosome 19. [125]. It has been shown to interact with NRF2, a transcription factor that regulates the expression of antioxidant proteins, leading to its ubiquitination and degradation in normal condition [125]. As response to oxidative stress, this process is inactivated, thus favouring nuclear factor erythroid 2–related factor 2-NRF2 action against oxidative damage [125]. *KEAP1* co-mutation is gaining relevance in the context of *EGFR*-mutated LUAD where it was found in about 20% of patients with advanced disease [126]. The resistance to oxidative stress accounts for resistance to radiotherapy. Moreover, this molecular alteration has also been associated with a premature failure of TKI response and a reduced sensitivity to osimertinib in *in vivo* models, thus suggesting an intrinsic resistance mechanism to TKI treatment [127]. An intriguing recent finding is about the combination of *KEAP1* and *TP53* mutations. In a study by Saleh et al. [128], the simultaneous detection of a p53 missense mutation in *KEAP1*-mutated LUAD improved patients' survival. In this complex scenario, TME could be called into question. Indeed, p53 is a negative regulator for NRF2 [125]. When mutated, it favours the production of reactive oxidative species and confers, as mentioned above, radio and chemoresistance, while on the other it increases the immunogenicity of the neoplasm [129].

5.5. Novelties from research studies

Although reported only in a few studies,[130,131], it appears to be research finding related to NSCLC the role of RBM10, a splicing factor, in the response to treatment. Nanjo et al. [131] performed functional studies in patient-derived lung cancer cell lines, assessing cell viability and apoptotic responses to Osimertinib. The authors suggested that RBM10 deficiency may limit the response of *EGFR*-mutant NSCLC to treatment. In the clinical setting, this means that patients with RBM10 deficiency may not respond well to standard treatments for this type of cancer [131]. However, the study also suggested that co-inhibition of Bcl-xL and *EGFR* mutant can overcome the resistance induced by RBM10 deficiency. [131]. RBM10 mutations co-occur in 7.6% of *EGFR* mutant NSCLC,[131], thus a significant portion of patients with *EGFR*-mutant NSCLC may also have RBM10 mutations, which could impact their response to treatment. More research is needed to confirm these findings and determine how they could be applied in clinical practice.

6. Co-mutations of concomitant actionable oncogenic drivers in *EGFR*-mutated LUAD

A special mention should be made of *EGFR*-mutated patients with co-occurring potentially oncogenic drivers.

Rarely, complex *EGFR* mutations can occur. The clinical significance of this association can be heterogenous. While the combination of a del19 with p.L858R in exons 19 and 21 respectively may enhance the TKI response, concurrent mutations in exons 18 and 20 lead to TKI resistance, as known for the T790M resistance mutation [132].

Although oncogene driver mutations are widely known as mutually exclusive, some cases of co-existent *EGFR, ALK, KRAS*, *ROS1,* and *BRAF* genetic alterations have been previously described, single or in multiple association occasionally [133]. While it is understandable how these co-mutations can result as a mechanism of resistance after treatment, the explanation in naive cases can be identified in tumour heterogeneity. In general, it seems that these cases of combined mutations confer some resistance to single TKI treatments, and usually poorer OS and PFS in comparison to single *EGFR* mutations. Because the cases series available so far are very limited or reported only as anecdotical case descriptions, one cannot yet reach definitive conclusions [132]. For *MET* amplification and *RET*, the knowledge is deeper. Indeed, both have been recognized as quite common secondary resistance mechanisms to TKI. As such, some clinical trials (SAVANNAH-NCT03778229 and ORCHARD-NCT03944772) are ongoing for combination strategies in these settings.

7. Unsolved issues and future perspectives

The genetic landscape of NSCLC is much more complicated than what is known so far, and this awareness will increase over time together with the development of new methodologies that allow a more precise characterization of co-mutations and possibly increased knowledge on their pathogenetic impact.

The intratumour molecular heterogeneity can have significant implications for the interpretation of NGS analysis, which is commonly used in clinical practice for cancer diagnosis and treatment. In particular, the presence of intratumour heterogeneity can limit the efficacy of targeted therapy, which relies on the identification of specific mutations or molecular alterations that are driving tumour growth. However, if the intratumour heterogeneity is properly characterized and understood, it can also serve as an interpretation key for NGS analysis. By identifying the different subclones within a tumour and their molecular profiles, clinicians can better tailor treatment regimens to the specific genetic makeup of the tumour and potentially improve treatment outcomes. In addition, addressing risk factors such as smoking cessation can potentially interfere with the natural history of the disease and reduce the overall burden of intratumour heterogeneity. For example, smoking cessation has been shown to reduce the risk of developing lung cancer and can potentially slow the progression of existing tumours by reducing the mutational burden and intratumour heterogeneity. Therefore, understanding and addressing intratumour molecular heterogeneity, both from a diagnostic and a prevention perspective, is pivotal for improving the efficacy of cancer treatments and ultimately reducing the overall burden of the disease.

While on one hand the progress in understanding the role of co-mutations is undeniable, on the other hand many unresolved issues have

emerged. Almost all studies are retrospective and based on a single centre-experience, recruiting a relatively small study population, which becomes even smaller when analysing the subgroups. Most studies focused on a histotype, preferentially LUAD, without a comprehensive histological evaluation. In this regard, it should be underlined that most diagnoses were performed before the last WHO classification, and this could have caused the neglect of some histological parameters (architectural pattern, grade, spread through air space, and vascular invasion) with recognized prognostic significance. A wide heterogeneity can easily be found when considering early and advanced stages taken together, as well as when considering *EGFR* mutations and co-mutations, indistinctly. Similarly, this is also true for the treatment that patients have undergone, which was different for drug, line, and sequence. Moreover, comparative studies between the baseline pre-treatment picture and post-treatment scenario are lacking.

Systematic evaluation and categorization of the full spectrum of co-mutations in NSCLC is certainly mandatory to elucidate the molecular and clinical diversity of tumours carrying out these alterations. The establishment of large representative multicentric databases of clinically sequenced NSCLC is the steppingstone for unravelling the mechanisms of resistance to targeted therapies. Prospective datasets, well-designed clinical trials, robust computational analyses, and functional studies on preclinical models are needed to translate these new insights into clinical practice and, lastly, towards the discovery and clinical validation of further actionable targets.

In conclusion, based on this emerging evidence, NSCLC patient outcomes may benefit from an increasingly granular molecular characterisation and, consequently, from more highly personalized therapeutic approaches.

CRediT authorship contribution statement

Federica Pezzuto: Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Véronique Hofman:** Investigation, Methodology, Formal analysis, Writing – review & editing. **Christophe Bontoux:** Formal analysis, Investigation, Methodology, Writing – review & editing. **Francesco Fortarezza:** Investigation, Methodology, Writing – review & editing. **Francesca Lunardi:** Formal analysis, Investigation, Methodology, Writing – review & editing. **Fiorella Calabrese:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – review & editing. **Paul Hofman:** Conceptualization, Formal analysis, Investigation, Data curation, Methodology, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Paul Hofman, MD, PhD received honorarium from AstraZeneca, Roche, Janssen, ThermoFisher Scientific, MSD, Biocartis, Novartis, Bayer, Abbvie, Qiagen, BMS and Pfizer. He participated to advisory boards for AstraZeneca, Roche, Janssen, ThermoFisher Scientific, MSD, Biocartis, Abbvie, Qiagen, Novartis, BMS and Pfizer.

Acknowledgements

Funding: This work was supported by University of Padova (BIRD218739/21).

References

[1] A.A. Thai, B.J. Solomon, L.V. Sequist, J.F. Gainor, R.S. Heist, Lung cancer, Lancet. 398 (10299) (2021) 535–554.
[2] WHO Classification of Tumours Editorial Board, Thoracic Tumours, 5th Ed., International Agency for Research on Cancer, Lyon, France, 2021.
[3] M. Chevallier, M. Borgeaud, A. Addeo, A. Friedlaender, Oncogenic driver mutations in non-small cell lung cancer: past, present and future, World J Clin Oncol 12 (4) (2021) 217–237.
[4] A.C. Tan, D.S.W. Tan, Targeted therapies for lung cancer patients with oncogenic driver molecular alterations, J Clin Oncol 40 (6) (2022) 611–625.
[5] Cancer Genome Atlas Research Network, Comprehensive molecular profiling of lung adenocarcinoma, Nature 511 (7511) (2014) 543–550.
[6] S. Kumar, J. Warrell, S. Li, P.D. McGillivray, W. Meyerson, L. Salichos, A. Harmanci, A. Martinez-Fundichely, C.W.Y. Chan, M.M. Nielsen, L. Lochovsky, Y. Zhang, X. Li, S. Lou, J.S. Pedersen, C. Herrmann, G. Getz, E. Khurana, M. B. Gerstein, Passenger mutations in more than 2,500 cancer genomes: overall molecular functional impact and consequences, Cell. 180 (5) (2020) 915–927. e16.
[7] N. Stransky, E. Cerami, S. Schalm, J.L. Kim, C. Lengauer, The landscape of kinase fusions in cancer, Nat Commun. 5 (2014) 1–10, https://doi.org/10.1038/ncomms5846.
[8] L.A. Garraway, E.S. Lander, Lessons from the cancer genome, Cell 153 (1) (2013) 17–37, https://doi.org/10.1016/j.cell.2013.03.002.
[9] R.J. Maggiore, E.K. Curran, M.E. Witt, D.J. Haraf, E. Everett, E.E.W. Cohen, Discovery and saturation analysis of cancer genes across 21 tumor types, Nature 4 (4) (2015) 327–333, https://doi.org/10.1038/nature12912.Discovery.
[10] D.A. Smith, Human genome sequencing, Science 233 (4770) (1986) 1246.
[11] W. Pao, N. Girard, New driver mutations in non-small-cell lung cancer, Lancet Oncol. 12 (2) (2011) 175–180, https://doi.org/10.1016/S1470-2045(10)70087-5.
[12] M.S. Lawrence, P. Stojanov, P. Polak, G.V. Kryukov, K. Cibulskis, A. Sivachenko, S.L. Carter, C. Stewart, C.H. Mermel, S.A. Roberts, A. Kiezun, P.S. Hammerman, A. McKenna, Y. Drier, L. Zou, A.H. Ramos, T.J. Pugh, N. Stransky, E. Helman, J. Kim, C. Sougnez, L. Ambrogio, E. Nickerson, E. Shefler, M.L. Cortés, D. Auclair, G. Saksena, D. Voet, M. Noble, D. DiCara, P. Lin, L. Lichtenstein, D.I. Heiman, T. Fennell, M. Imielinski, B. Hernandez, E. Hodis, S. Baca, A.M. Dulak, J. Lohr, D. A. Landau, C.J. Wu, J. Melendez-Zajgla, A. Hidalgo-Miranda, A. Koren, S. A. McCarroll, J. Mora, B. Crompton, R. Onofrio, M. Parkin, W. Winckler, K. Ardlie, S.B. Gabriel, C.W.M. Roberts, J.A. Biegel, K. Stegmaier, A.J. Bass, L. A. Garraway, M. Meyerson, T.R. Golub, D.A. Gordenin, S. Sunyaev, E.S. Lander, G. Getz, Mutational heterogeneity in cancer and the search for new cancer-associated genes, Nature. 499 (7457) (2013) 214–218.
[13] P. Liu, C. Morrison, L. Wang, D. Xiong, P. Vedell, P. Cui, X. Hua, F. Ding, Y. Lu, M. James, J.D. Ebben, H. Xu, A.A. Adjei, K. Head, J.W. Andrae, M.R. Tschannen, H. Jacob, J. Pan, Q.i. Zhang, F. Van den Bergh, H. Xiao, K.C. Lo, J. Patel, T. Richmond, M.-A. Watt, T. Albert, R. Selzer, M. Anderson, J. Wang, Y. Wang, S. Starnes, P. Yang, M. You, Identification of somatic mutations in non-small cell lung carcinomas using whole-exome sequencing, Carcinogenesis 33 (7) (2012) 1270–1276.
[14] X.-J. Yu, M.-J. Yang, B.o. Zhou, G.-Z. Wang, Y.-C. Huang, L.-C. Wu, X. Cheng, Z.-S. Wen, J.-Y. Huang, Y.-D. Zhang, X.-H. Gao, G.-F. Li, S.-W. He, Z.-H. Gu, L. Ma, C.-M. Pan, P. Wang, H.-B. Chen, Z.-P. Hong, X.-L. Wang, W.-J. Mao, X.-L. Jin, H. Kang, S.-T. Chen, Y.-Q. Zhu, W.-Y. Gu, Z.i. Liu, H. Dong, L.-W. Tian, S.-J. Chen, Y.i. Cao, S.-Y. Wang, G.-B. Zhou, Characterization of Somatic Mutations in Air Pollution-Related Lung Cancer, EBioMedicine 2 (6) (2015) 583–590.
[15] S. Ilango, B. Paital, P. Jayachandran, P. Raghunathan, R. Nirmaladevi, Epigenetic alterations in cancer Department of Biochemistry, Biotechnology and Bioinformatics, Avinashilingam Institute for Home Science and Higher Education for Women, Coimbatore, 641043, Tamil Nadu, India, 2 Redox Regulation Laboratory, Departme. Front Biosci. 25 (2020) 1058–1109.
[16] M.F. Senosain, Massion pp., Intratumor Heterogeneity in Early Lung Adenocarcinoma, Front Oncol. 10 (March) (2020) 1–9.
[17] Endesfelder D, Math D, Gronroos E, et al. new england journal. 2012.
[18] F.Z. Marino, R. Bianco, M. Accardo, A. Ronchi, I. Cozzolino, F. Morgillo, G. Rossi, R. Franco, Molecular heterogeneity in lung cancer: from mechanisms of origin to clinical implications, Int J Med Sci. 16 (7) (2019) 981–989.
[19] A. Friedlaender, P. Tsantoulis, M. Chevallier, C. De Vito, A. Addeo, The Impact of Variant Allele Frequency in EGFR Mutated NSCLC Patients on Targeted Therapy, Front Oncol 11 (2021), 644472.
[20] F. Skoulidis, J.V. Heymach, Co-occurring genomic alterations in non-small-cell lung cancer biology and therapy, Nat Rev Cancer 19 (9) (2019) 495–509.
[21] J.W. Riess, D.R. Gandara, G.M. Frampton, R. Madison, N. Peled, J.A. Bufill, G. K. Dy, S.-H. Ou, P.J. Stephens, J.D. McPherson, P.N. Lara, R.A. Burich, J.S. Ross, V.A. Miller, S.M. Ali, P.C. Mack, A.B. Schrock, Diverse EGFR Exon 20 Insertions and Co-Occurring Molecular Alterations Identified by Comprehensive Genomic Profiling of NSCLC, J Thorac Oncol 13 (10) (2018) 1560–1568.
[22] C.M. Blakely, T.B.K. Watkins, W. Wu, B. Gini, J.J. Chabon, C.E. McCoach, N. McGranahan, G.A. Wilson, N.J. Birkbak, V.R. Olivas, J. Rotow, A. Maynard, V. Wang, M.A. Gubens, K.C. Banks, R.B. Lanman, A.F. Caulin, J. St John, A. R. Cordero, P. Giannikopoulos, A.D. Simmons, P.C. Mack, D.R. Gandara, H. Husain, R.C. Doebele, J.W. Riess, M. Diehn, C. Swanton, T.G. Bivona, Evolution and clinical impact of co-occurring genetic alterations in advanced-stage EGFR-mutant lung cancers, Nat Genet 49 (12) (2017) 1693–1704.
[23] T. Ozaki, A. Nakagawara, Role of p53 in cell death and human cancers, Cancers (Basel) 3 (1) (2011) 994–1013.
[24] C. Venot, M. Maratrat, C. Dureuil, E. Conseiller, L. Bracco, L. Debussche, The requirement for the p53 proline-rich functional domain for mediation of apoptosis is correlated with specific PIG3 gene transactivation and with transcriptional repression, EMBO J 17 (16) (1998) 4668–4679.

[25] S. Larsen, T. Yokochi, E. Isogai, Y. Nakamura, T. Ozaki, A. Nakagawara, LMO3 interacts with p53 and inhibits its transcriptional activity, Biochem Biophys Res Commun 392 (3) (2010) 252–257.
[26] K.L. Harms, X. Chen, The C Terminus of p53 Family Proteins Is a Cell Fate Determinant, Mol Cell Biol. 25 (5) (2005) 2014–2030.
[27] A. Willis, E.J. Jung, T. Wakefield, X. Chen, Mutant p53 exerts a dominant negative effect by preventing wild-type p53 from binding to the promoter of its target genes, Oncogene. 23 (13) (2004) 2330–2338.
[28] M. Subramanian, M. Jones, A. Lal, Long non-coding RNAs embedded in the Rb and p53 pathways, Cancers (Basel). 5 (4) (2013) 1655–1675.
[29] C. Mao, X. Wang, Y. Liu, et al., HHS Public Access. 78 (13) (2021) 3484–3496, https://doi.org/10.1158/0008-5472.CAN-17-3454.A.
[30] M. Wang, C. Mao, L. Ouyang, Y. Liu, W. Lai, N.a. Liu, Y. Shi, L. Chen, D. Xiao, F. Yu, X. Wang, H.u. Zhou, Y.a. Cao, S. Liu, Q. Yan, Y. Tao, B. Zhang, Long noncoding RNA LINC00336 inhibits ferroptosis in lung cancer by functioning as a competing endogenous RNA, Cell Death Differ. 26 (11) (2019) 2329–2343.
[31] S.J. Klug, M. Ressing, J. Koenig, M.C. Abba, T. Agorastos, S.MF. Brenna, M. Ciotti, B.R. Das, A. Del Mistro, A. Dybikowska, A.R. Giuliano, Z. Gudleviciene, U. Gyllensten, A.LF. Haws, A. Helland, C.S. Herrington, A. Hildesheim, O. Humbey, S.H. Jee, J.W. Kim, M.M. Madeleine, J. Menczer, H.YS. Ngan, A. Nishikawa, Y. Niwa, R. Pegoraro, M.R. Pillai, G. Ranzani, G. Rezza, A. N. Rosenthal, S. Roychoudhury, D. Saranath, V.M. Schmitt, S. Sengupta, W. Settheetham-Ishida, H. Shirasawa, P.JF. Snijders, M.H. Stoler, A.E. Suárez-Rincón, K. Szarka, R. Tachezy, M. Ueda, A.GJ. van der Zee, M. von Knebel Doeberitz, M.-T. Wu, T. Yamashita, I. Zehbe, M. Blettner, TP53 codon 72 polymorphism and cervical cancer: a pooled analysis of individual data from 49 studies, Lancet Oncol. 10 (8) (2009) 772–784.
[32] S. Alawadi, L. Ghabreau, M. Alsaleh, Z. Abdulaziz, M. Rafeek, N. Akil, M. Alkhalaf, P53 gene polymorphisms and breast cancer risk in Arab women, Med Oncol. 28 (3) (2011) 709–715.
[33] H. Yu, Y.-J. Huang, Z. Liu, L.-E. Wang, G. Li, E.M. Sturgis, D.G. Johnson, Q. Wei, Effects of MDM2 promoter polymorphisms and p53 codon 72 polymorphism on risk and age at onset of squamous cell carcinoma of the head and neck, Mol Carcinog. 50 (9) (2011) 697–706.
[34] J.-M. Piao, H.N. Kim, H.-R. Song, S.-S. Kweon, J.-S. Choi, W.-J. Yun, Y.-C. Kim, I.-J. Oh, K.-S. Kim, M.-H. Shin, P53 codon 72 polymorphism and the risk of lung cancer in a Korean population, Lung Cancer. 73 (3) (2011) 264–267.
[35] J.-J. Wang, Y. Zheng, L. Sun, L.i. Wang, P.-B. Yu, J.-H. Dong, L. Zhang, J. Xu, W. Shi, Y.-C. Ren, TP53 codon 72 polymorphism and colorectal cancer susceptibility: A meta-analysis, Mol Biol Rep. 38 (8) (2011) 4847–4853.
[36] D.-K. Jiang, L. Yao, W.-H. Ren, W.-Z. Wang, B.o. Peng, L. Yu, TP53 Arg72Pro polymorphism and endometrial cancer risk: A meta-analysis, Med Oncol. 28 (4) (2011) 1129–1135.
[37] H.S. Thurow, R. Haack, F.P. Hartwig, I.O. de Oliveira, O.A. Dellagostin, D. P. Gigante, B.L. Horta, T. Collares, F.K. Seixas, TP53 gene polymorphism: Importance to cancer, ethnicity and birth weight in a Brazilian cohort, J Biosci. 36 (5) (2011) 823–831.
[38] C.-Y. Huang, C.-T. Su, J.-S. Chu, S.-P. Huang, Y.-S. Pu, H.-Y. Yang, C.-J. Chung, C.-C. Wu, Y.-M. Hsueh, The polymorphisms of P53 codon 72 and MDM2 SNP309 and renal cell carcinoma risk in a low arsenic exposure area, Toxicol Appl Pharmacol. 257 (3) (2011) 349–355.
[39] M.L. Poeta, J. Manola, M.A. Goldwasser, A. Forastiere, N. Benoit, J.A. Califano, J. A. Ridge, J. Goodwin, D. Kenady, J. Saunders, W. Westra, D. Sidransky, W. M. Koch, TP53 Mutations and Survival in Squamous-Cell Carcinoma of the Head and Neck, N Engl J Med. 357 (25) (2007) 2552–2561.
[40] R. Govindan, J. Weber, TP53 mutations and lung cancer: Not all mutations are created equal, Clin Cancer Res. 20 (17) (2014) 4419–4421.
[41] M.A. Molina-Vila, J. Bertran-Alamillo, A. Gascó, C. Mayo-de-las-Casas, M. Sánchez-Ronco, L. Pujantell-Pastor, L Bonanno, A.G. Favaretto, A.F. Cardona, A. Vergnenègre, M. Majem, B. Massuti, T. Morán, E. Carcereny, S. Viteri, R. Rosell, Nondisruptive p53 mutations are associated with shorter survival in patients with advanced non-small cell lung cancer, Clin Cancer Res 20 (17) (2014) 4647–4659.
[42] A.R. Halvorsen, L. Silwal-Pandit, L.A. Meza-Zepeda, D. Vodak, P. Vu, C. Sagerup, E. Hovig, O. Myklebost, A.-L. Børresen-Dale, O.T. Brustugun, Å. Helland, TP53 mutation spectrum in smokers and never smoking lung cancer patients, Front Genet. 07 (2016) 85.
[43] S.M. Lim, H.R. Kim, E.K. Cho, Y.J. Min, J.S. Ahn, M.-J. Ahn, K. Park, B.C. Cho, J.-H. Lee, H.C. Jeong, E.K. Kim, J.-H. Kim, Targeted sequencing identifies genetic alterations that confer Primary resistance to EGFR tyrosine kinase inhibitor (Korean Lung Cancer Consortium), Oncotarget. 7 (24) (2016) 36311–36320.
[44] Y. Jin, X. Shi, J. Zhao, Q. He, M. Chen, J. Yan, Q. Ou, X. Wu, Y.W. Shao, X. Yu, Mechanisms of primary resistance to EGFR targeted therapy in advanced lung adenocarcinomas, Lung Cancer. 124 (2018) 110–116.
[45] J.N. Jakobsen, E. Santoni-Rugiu, M. Grauslund, L. Melchior, J.B. Sørensen, Concomitant driver mutations in advanced EGFR-mutated nonsmall- cell lung cancer and their impact on erlotinib treatment, Oncotarget. 9 (40) (2018) 26195–26208.
[46] S. Michels, C. Heydt, B. van Veggel, B. Deschler-Baier, N. Pardo, K. Monkhorst, V. Rüsseler, J. Stratmann, F. Griesinger, S. Steinhauser, A. Kostenko, J. Diebold, J. Fassunke, R. Fischer, W. Engel-Riedel, O. Gautschi, E. Geissinger, S. Haneder, M.A. Ihle, H.-G. Kopp, A.J. de Langen, A. Martinez-Marti, L. Nogova, T. Persigehl, D. Plenker, M. Puesken, E. Rodermann, A. Rosenwald, A.H. Scheel, M. Scheffler, W. Spengler, R. Seggewiss-Bernhardt, J. Brägelmann, M. Sebastian, B. Vrugt, M. Hellmich, M.L. Sos, L.C. Heukamp, E. Felip, S. Merkelbach-Bruse, E.F. Smit, R. Büttner, J. Wolf, Genomic Profiling Identifies Outcome-Relevant Mechanisms of Innate and Acquired Resistance to Third-Generation Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy in Lung Cancer, JCO Precis Oncol. (3) (2019) 1–14.
[47] H. Chen, M. Liu, Z. Dai, S. Li, Y. Luo, Y. Wang, W. Su, W. Cai, D. Yang, J. Huang, Z. Yang, Concomitant genetic alterations are associated with response to EGFR targeted therapy in patients with lung adenocarcinoma, Transl Lung Cancer Res. 9 (4) (2020) 1225–1234.
[48] J. Roeper, M. Falk, A. Chalaris-Rißmann, A.C. Lueers, H. Ramdani, K. Wedeken, U. Stropiep, L. Diehl, M. Tiemann, L.C. Heukamp, F. Otto-Sobotka, F. Griesinger, TP53 co-mutations in EGFR mutated patients in NSCLC stage IV: A strong predictive factor of ORR, PFS and OS in EGFR mt+ NSCLC, Oncotarget. 11 (3) (2020) 250–264.
[49] Y. Zhao, Y. Pan, C. Cheng, D. Zheng, Y. Zhang, Z. Gao, F. Fu, H. Li, S. Zheng, L. Zhuge, H. Mao, M. Kuang, X. Tao, Y. Peng, H. Hu, J. Xiang, Y. Li, Y. Sun, H. Chen, EGFR-mutant lung adenocarcinoma harboring co-mutational tumor suppressor genes predicts poor prognosis, J Cancer Res Clin Oncol. 146 (7) (2020) 1781–1789.
[50] K. Jao, P. Tomasini, S. Kamel-Reid, G.J. Korpanty, C. Mascaux, S. Sakashita, C. Labbé, N.B. Leighl, G. Liu, R. Feld, P.A. Bradbury, D.M. Hwang, M. Pintilie, M.-S. Tsao, F.A. Shepherd, The prognostic effect of single and multiple cancer-related somatic mutations in resected non-small-cell lung cancer, Lung Cancer. 123 (2018) 22–29.
[51] Y.-X. Shi, D.-Q. Sheng, L. Cheng, X.-Y. Song, Current Landscape of Epigenetics in Lung Cancer: Focus on the Mechanism and Application, J Oncol. 2019 (2019) 1–11.
[52] S.S. Hung, B. Meissner, E.A. Chavez, S. Ben-Neriah, D. Ennishi, M.R. Jones, H. P. Shulha, F.C. Chan, M. Boyle, R. Kridel, R.D. Gascoyne, A.J. Mungall, M. A. Marra, D.W. Scott, J.M. Connors, C. Steidl, Assessment of Capture and Amplicon-Based Approaches for the Development of a Targeted Next-Generation Sequencing Pipeline to Personalize Lymphoma Management, J Mol Diagnostics. 20 (2) (2018) 203–214.
[53] C. Aggarwal, C.W. Davis, R. Mick, J.C. Thompson, S. Ahmed, S. Jeffries, S. Bagley, P. Gabriel, T.L. Evans, J.M. Bauml, C. Ciunci, E. Alley, J.J.D. Morrissette, R. B. Cohen, E.L. Carpenter, C.J. Langer, Influence of TP53 Mutation on Survival in Patients With Advanced EGFR -Mutant Non–Small-Cell Lung Cancer, JCO Precis Oncol. (2) (2018) 1–29.
[54] D.L. Aisner, L.M. Sholl, L.D. Berry, M.R. Rossi, H. Chen, J. Fujimoto, A.L. Moreira, S. Ramalingam, L.C. Villaruz, G.A. Otterson, E. Haura, K. Politi, B. Glisson, J. Cetnar, E.B. Garon, J. Schiller, S.N. Waqar, L.V. Sequist, J. Brahmer, Y. Shyr, K. Kugler, I.I. Wistuba, B.E. Johnson, J.D. Minna, M.G. Kris, P.A. Bunn, D. J. Kwiatkowski, The impact of smoking and tp53 mutations in lung adenocarcinoma patients with targetable mutations—the lung cancer mutation consortium (LCMC2), Clin Cancer Res. 24 (5) (2018) 1038–1047.
[55] R. Zhang, P. Tian, B. Chen, T. Wang, W. Li, The prognostic impact of TP53 comutation in EGFR mutant lung cancer patients: a systematic review and meta-analysis, Postgrad Med. 131 (3) (2019) 199–206.
[56] H. Hou, K. Qin, Y. Liang, C. Zhang, D. Liu, H. Jiang, K. Liu, J. Zhu, H. Lv, T. Li, Concurrent TP53 mutations predict poor outcomes of EGFR-TKI treatments in chinese patients with advanced nsclc, Cancer Manag Res 21 (11) (2019) 5665–5675.
[57] M. Canale, E. Petracci, A. Delmonte, G. Bronte, E. Chiadini, V. Ludovini, A. Dubini, M. Papi, S. Baglivo, N. De Luigi, A. Verlicchi, R. Chiari, L. Landi, G. Metro, M.A. Burgio, L. Crinò, P. Ulivi, Concomitant TP53 mutation confers worse prognosis in EGFR-mutated non-small cell lung cancer patients treated with TKIs, J Clin Med. 9 (4) (2020) 1047.
[58] K. Qin, H. Hou, Y.u. Liang, X. Zhang, Prognostic value of TP53 concurrent mutations for EGFR- TKIs and ALK-TKIs based targeted therapy in advanced non-small cell lung cancer: A meta-analysis, BMC Cancer 20 (1) (2020) 328.
[59] A. Passaro, I. Attili, A. Rappa, D. Vacirca, A. Ranghiero, C. Fumagalli, J. Guarize, L. Spaggiari, F. de Marinis, M. Barberis, E. Guerini-Rocco, Genomic characterization of concurrent alterations in non-small cell lung cancer (Nsclc) harboring actionable mutations, Cancers (Basel). 13 (9) (2021) 2172.
[60] W. Lv, H. Cheng, D.i. Shao, Y. Wei, W. Zhu, K. Wu, W. Jiang, L. Hu, Z. Sha, B. Zhong, X. Pei, Treatment Patterns and Survival of Patients With Advanced Non-Small Cell Lung Cancer Guided by Comprehensive Genomic Profiling: Real-World Single-Institute Study in China, Front Oncol 11 (2021), 630717.
[61] D.W.Y. Tsui, M. Murtaza, A.S.C. Wong, O.M. Rueda, C.G. Smith, D. Chandrananda, R.A. Soo, H.L. Lim, B.C. Goh, C. Caldas, T. Forshew, D. Gale, W. Liu, J. Morris, F. Marass, T. Eisen, T.M. Chin, N. Rosenfeld, Dynamics of multiple resistance mechanisms in plasma DNA during EGFR-targeted therapies in non-small cell lung cancer, EMBO Mol Med. 10 (6) (2018), https://doi.org/10.15252/emmm.201707945.
[62] F. Wang, N. Zhao, G.e. Gao, H.-B. Deng, Z.-H. Wang, L.-L. Deng, Y.u. Yang, C. Lu, Prognostic value of TP53 co-mutation status combined with EGFR mutation in patients with lung adenocarcinoma, J Cancer Res Clin Oncol. 146 (11) (2020) 2851–2859.
[63] Y. Cheng, L. Ma, Y. Liu, J. Zhu, Y. Xin, X. Liu, Y. Wang, T. Zhang, C. Yang, S. Wang, H. Cui, L. Zhang, J. Dai, L. Shao, J. Lin, J. Ye, H. Liu, Comprehensive characterization and clinical impact of concomitant genomic alterations in EGFR-mutant NSCLCs treated with EGFR kinase inhibitors, Lung Cancer. 145 (2020) 63–70.
[64] E. Iwama, K. Sakai, K. Azuma, D. Harada, K. Nosaki, K. Hotta, M. Nishio, T. Kurata, T. Fukuhara, H. Akamatsu, K. Goto, T. Shimose, J. Kishimoto, Y. Nakanishi, K. Nishio, I. Okamoto, Exploration of resistance mechanisms for epidermal growth factor receptor-tyrosine kinase inhibitors based on plasma

analysis by digital polymerase chain reaction and next-generation sequencing, Cancer Sci. 109 (12) (2018) 3921–3933.
[65] C. Labbé, M. Cabanero, G.J. Korpanty, P. Tomasini, M.K. Doherty, C. Mascaux, K. Jao, B. Pitcher, R. Wang, M. Pintilie, N.B. Leighl, R. Feld, G. Liu, P.A. Bradbury, S. Kamel-Reid, M.-S. Tsao, F.A. Shepherd, Prognostic and predictive effects of TP53 co-mutation in patients with EGFR-mutated non-small cell lung cancer (NSCLC), Lung Cancer. 111 (2017) 23–29.
[66] P.A. VanderLaan, D. Rangachari, S.M. Mockus, V. Spotlow, H.V. Reddi, J. Malcolm, M.S. Huberman, L.J. Joseph, S.S. Kobayashi, D.B. Costa, Mutations in TP53, PIK3CA, PTEN and other genes in EGFR mutated lung cancers: Correlation with clinical outcomes, Lung Cancer. 106 (2017) 17–21.
[67] Y. Kim, B. Lee, J.H. Shim, S.-H. Lee, W.-Y. Park, Y.-L. Choi, J.-M. Sun, J.S. Ahn, M.-J. Ahn, K. Park, Concurrent Genetic Alterations Predict the Progression to Target Therapy in EGFR-Mutated Advanced NSCLC, J Thorac Oncol. 14 (2) (2019) 193–202.
[68] H.A. Yu, K. Suzawa, E. Jordan, A. Zehir, A. Ni, R. Kim, M.G. Kris, N.D. Hellmann, B.T. Li, R. Somwar, D.B. Solit, M.F. Berger, M. Arcila, G.J. Riely, M. Ladanyi, Concurrent Alterations in EGFR-Mutant Lung Cancers Associated with Resistance to EGFR Kinase Inhibitors and Characterization of MTOR as a Mediator of Resistance, Clin Cancer Res. 24 (13) (2018) 3108–3118.
[69] Y.W. Choi, S.Y. Jeon, G.S. Jeong, H.W. Lee, S.H. Jeong, S.Y. Kang, J.S. Park, J.-H. Choi, Y.W. Koh, J.H. Han, S.S. Sheen, EGFR Exon 19 Deletion is Associated with Favorable Overall Survival after First-line Gefitinib Therapy in Advanced Non-Small Cell Lung Cancer Patients, Am J Clin Oncol Cancer Clin Trials. 41 (4) (2018) 385–390.
[70] Y. Wei, K. Shen, T. Lv, X. Wang, C. Li, H. Fan, Y. Lv, H. Liu, Y. Song, Three new disease-progression modes in NSCLC patients after EGFR-TKI treatment by next-generation sequencing analysis, Lung Cancer. 125 (2018) 43–50.
[71] A. Rachiglio, F. Fenizia, M. Piccirillo, D. Galetta, L. Crinò, B. Vincenzi, E. Barletta, C. Pinto, F. Ferraù, M. Lambiase, A. Montanino, C. Roma, V. Ludovini, E. Montagna, A. De, G. Luca, G. Rocco, F. Botti, A. Perrone, N. Morabito, Normanno The Presence of Concomitant Mutations Affects the Activity of EGFR Tyrosine Kinase Inhibitors in EGFR-Mutant Non-Small Cell Lung Cancer (NSCLC) Patients, Cancers. 11 (3) (2019) 341.
[72] S. Wang, M. Jiang, Z. Yang, X. Huang, N. Li, The role of distinct co-mutation patterns with TP53 mutation in immunotherapy for NSCLC, Genes Dis. 9 (1) (2022) 245–251.
[73] C.M.J. Steendam, G.D.M. Veerman, M.A. Pruis, P. Atmodimedjo, M.S. Paats, C. van der Leest, J.H. von der Thüsen, D.C.Y. Yick, E. Oomen-de Hoop, S.L. W. Koolen, W.N.M. Dinjens, R.H.N. van Schaik, R.H.J. Mathijssen, J.G.J.V. Aerts, H.J. Dubbink, A.-M. Dingemans, Plasma predictive features in treating egfr-mutated non-small cell lung cancer, Cancers (Basel). 12 (11) (2020) 3179.
[74] Y. Jin, H. Bao, X. Le, X. Fan, M. Tang, X. Shi, J. Zhao, J. Yan, Y. Xu, K. Quek, Y. Y. Elamin, J. Zhang, P.A. Futreal, I.I. Wistuba, J.V. Heymach, G. Lou, L. Shao, Q. He, C. Lin, X. Wu, Y.W. Shao, X. Wang, J. He, Y. Chen, J. Stebbing, M. Chen, J. Zhang, X. Yu, Distinct co-acquired alterations and genomic evolution during TKI treatment in non-small-cell lung cancer patients with or without acquired T790M mutation, Oncogene. 39 (9) (2020) 1846–1859.
[75] E. Bria, S. Pilotto, E. Amato, M. Fassan, S. Novello, U. Peretti, T. Vavalà, S. Kinspergher, L. Righi, A. Santo, M. Brunelli, V. Corbo, E. Giglioli, I. Sperduti, M. Milella, M. Chilosi, A. Scarpa, G. Tortora, Molecular heterogeneity assessment by next-generation sequencing and response to gefitinib of EGFR mutant advanced lung adenocarcinoma, Oncotarget. 6 (14) (2015) 12783–12795.
[76] J. Tan, C. Hu, P. Deng, R. Wan, L. Cao, M. Li, H. Yang, Q. Gu, J. An, J. Jiang, The Predictive Values of Advanced Non-Small Cell Lung Cancer Patients Harboring Uncommon EGFR Mutations—The Mutation Patterns, Use of Different Generations of EGFR-TKIs, and Concurrent Genetic Alterations, Front Oncol. 11 (2021), https://doi.org/10.3389/fonc.2021.646577.
[77] Z. Yang, Y.a. Chen, Y. Wang, S. Wang, M. Hu, B.o. Zhang, B. Han, Efficacy of EGFR-TKI Plus Chemotherapy or Monotherapy as First-Line Treatment for Advanced EGFR-Mutant Lung Adenocarcinoma Patients With Co-Mutations, Front Oncol. 11 (2021), https://doi.org/10.3389/fonc.2021.681429.
[78] Y. Xu, X. Tong, J. Yan, X. Wu, Y.W. Shao, Y. Fan, Short-Term Responders of Non-Small Cell Lung Cancer Patients to EGFR Tyrosine Kinase Inhibitors Display High Prevalence of TP53 Mutations and Primary Resistance Mechanisms, Transl Oncol. 11 (6) (2018) 1364–1369.
[79] M. Chen, Y. Xu, J. Zhao, W. Zhong, L.i. Zhang, Y. Bi, M. Wang, concurrent driver gene mutations as negative predictive factors in epidermal growth factor receptor-positive non-small cell lung cancer, EBioMedicine. 42 (2019) 304–310.
[80] P. Christopoulos, M. Kirchner, J. Roeper, F. Saalfeld, M. Janning, F. Bozorgmehr, N. Magios, D. Kazdal, A.L. Volckmar, L.M. Brückner, T. Bochtler, M. Kriegsmann, V. Endris, R. Penzel, K. Kriegsmann, M. Eichhorn, F.J.F. Herth, C.P. Heussel, R. A. El Shafie, M.A. Schneider, T. Muley, M. Meister, M. Faehling, J.R. Fischer, L. Heukamp, P. Schirmacher, H. Bischoff, M. Wermke, S. Loges, F. Griesinger, A. Stenzinger, M. Thomas, Risk stratification of EGFR+ lung cancer diagnosed with panel-based next-generation sequencing, Lung Cancer. 148 (2020) 105–112.
[81] N. Yamamoto, T. Seto, M. Nishio, K. Goto, N. Yamamoto, I. Okamoto, T. Yamanaka, M. Tanaka, K. Takahashi, M. Fukuoka, Erlotinib plus bevacizumab vs erlotinib monotherapy as first-line treatment for advanced EGFR mutation-positive non-squamous non-small-cell lung cancer: survival follow-up results of the randomized JO25567 study, Lung Cancer. 151 (2021) 20–24.
[82] X.-M. Li, W.-F. Li, J.-T. Lin, H.-H. Yan, H.-Y. Tu, H.-J. Chen, B.-C. Wang, Z. Wang, Q. Zhou, X.-C. Zhang, J. Su, R.-L. Chen, Y.-L. Wu, J.-J. Yang, Predictive and Prognostic Potential of TP53 in Patients With Advanced Non–Small-Cell Lung Cancer Treated With EGFR-TKI: Analysis of a Phase III Randomized Clinical Trial (CTONG 0901), Clin Lung Cancer 22 (2) (2021) 100–109.e3.
[83] J. Roeper, P. Christopoulos, M. Falk, L.C. Heukamp, M. Tiemann, A. Stenzinger, M. Thomas, F. Griesinger, TP53 co-mutations as an independent prognostic factor in 2nd and further line therapy—EGFR mutated non-small cell lung cancer IV patients treated with osimertinib, Transl Lung Cancer Res. 11 (1) (2022) 4–13.
[84] M. Canale, E. Petracci, A. Delmonte, et al., Impact of TP53 mutations on outcome in EGFR-mutated patients treated with first-line tyrosine kinase inhibitors, Clin Cancer Res 23 (9) (2017) 2195–2202.
[85] N.I. Vokes, E. Chambers, T. Nguyen, A. Coolidge, C.A. Lydon, X. Le, L. Sholl, J. V. Heymach, M. Nishino, E.M. Van Allen, P.A. Jänne, Concurrent TP53 Mutations Facilitate Resistance Evolution in EGFR-Mutant Lung Adenocarcinoma, J Thorac Oncol. 17 (6) (2022) 779–792.
[86] S.S. Ramalingam, J. Vansteenkiste, D. Planchard, B.C. Cho, J.E. Gray, Y. Ohe, C. Zhou, T. Reungwetwattana, Y. Cheng, B. Chewaskulyong, R. Shah, M. Cobo, K. H. Lee, P. Cheema, M. Tiseo, T. John, M.-C. Lin, F. Imamura, T. Kurata, A. Todd, R. Hodge, M. Saggese, Y. Rukazenkov, J.-C. Soria, Overall Survival with Osimertinib in Untreated, EGFR -Mutated Advanced NSCLC, N Engl J Med. 382 (1) (2020) 41–50.
[87] X. Le, C. Molife, M.S. Leusch, M.T. Rizzo, P.M. Peterson, N. Caria, Y. Chen, E. G. Gugel, C. Visseren-Grul, TP53 Co-Mutation Status Association with Clinical Outcomes in Patients with EGFR-Mutant Non-Small Cell Lung Cancer, Cancers (Basel) 14 (24) (2022) 6127.
[88] F. Hao, L. Gu, D. Zhong, TP53 Mutation Mapping in Advanced Non-Small Cell Lung Cancer: A Real-World Retrospective Cohort Study, Curr Oncol. 29 (10) (2022) 7411–7419, https://doi.org/10.3390/curroncol29100582.
[89] W. Jiang, H. Cheng, Y.u. Lili, J. Zhang, Y. Wang, Y. Liang, F. Lou, S.C. Huina Wang, Mutation patterns and evolutionary action score of TP53 enable identification of a patient population with poor prognosis in advanced non-small cell lung cancer, Cancer Med. 12 (6) (2022) 6649–6658.
[90] C. Zheng, X. Li, Y. Ren, Z. Yin, B. Zhou, Coexisting EGFR and TP53 Mutations in Lung Adenocarcinoma Patients Are Associated With COMP and ITGB8 Upregulation and Poor Prognosis, Front Mol Biosci 7 (30) (2020), https://doi.org/10.3389/fmolb.2020.00030.
[91] C.-K. Lee, S. Kim, J.S. Lee, J.E. Lee, S.-M. Kim, I.S. Yang, H.R. Kim, J.H. Lee, S. Kim, B.C. Cho, Next-generation sequencing reveals novel resistance mechanisms and molecular heterogeneity in EGFR-mutant non-small cell lung cancer with acquired resistance to EGFR-TKIs, Lung Cancer 113 (2017) 106–114.
[92] T. Olivier, V. Prasad, Amivantamab and Mobocertinib in Exon 20 insertions EGFR Mutant Lung Cancer, Challenge To The Current Guidelines, Transl Oncol. 23 (June) (2022) 27–29, https://doi.org/10.1016/j.tranon.2022.101475.
[93] H. Udagawa, S. Hasako, A. Ohashi, R. Fujioka, Y. Hakozaki, M. Shibuya, N. Abe, T. Komori, T. Haruma, M. Terasaka, R. Fujita, A. Hashimoto, K. Funabashi, H. Yasuda, K. Miyadera, K. Goto, D.B. Costa, S.S. Kobayashi, TAS6417/CLN-081 Is a Pan-Mutation-Selective EGFR Tyrosine Kinase Inhibitor with a Broad Spectrum of Preclinical Activity against Clinically Relevant EGFR MutationsM, Mol Cancer Res. 17 (11) (2019) 2233–2243.
[94] D.V. Ganesha, R. Naik, S.S. Mufti, H. Varayathu, Molecular Therapeutics of Non-Small Cell Lung Cancer (NSCLC) and Challenges in Repeat Tissue Biopsy, Adv Lung Cancer 10 (03) (2021) 21–39.
[95] N. Girard, A. Minchom, S.-H. Ou, S.M. Gadgeel, J. Trigo, S. Viteri, J.M. Bauml, A. Londhe, P. Mahadevia, L. Bazhenova, Comparative Clinical Outcomes Between EGFR Ex20ins and Wildtype NSCLC Treated with Immune Checkpoint Inhibitors, Clin Lung Cancer. 23 (7) (2022) 571–577.
[96] K. Hastings, H.A. Yu, W. Wei, F. Sanchez-Vega, M. DeVeaux, J. Choi, H. Rizvi, A. Lisberg, A. Truini, C.A. Lydon, Z. Liu, B.S. Henick, A. Wurtz, G. Cai, A. J. Plodkowski, N.M. Long, D.F. Halpenny, J. Killam, I. Oliva, N. Schultz, G. J. Riely, M.E. Arcila, M. Ladanyi, D. Zelterman, R.S. Herbst, S.B. Goldberg, M. M. Awad, E.B. Garon, S. Gettinger, M.D. Hellmann, K. Politi, EGFR mutation subtypes and response to immune checkpoint blockade treatment in non-small-cell lung cancer, Ann Oncol. 30 (8) (2019) 1311–1320.
[97] H. Borghaei, L. Paz-Ares, L. Horn, D.R. Spigel, M. Steins, N.E. Ready, L.Q. Chow, E.E. Vokes, E. Felip, E. Holgado, F. Barlesi, M. Kohlhäufl, O. Arrieta, M.A. Burgio, J. Fayette, H. Lena, E. Poddubskaya, D.E. Gerber, S.N. Gettinger, C.M. Rudin, N. Rizvi, L. Crinò, G.R. Blumenschein, S.J. Antonia, C. Dorange, C.T. Harbison, F. Graf Finckenstein, J.R. Brahmer, Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer, N Engl J Med. 373 (17) (2015) 1627–1639.
[98] M. Muller, R.D. Schouten, C.J. De Gooijer, P. Baas, Pembrolizumab for the treatment of non-small cell lung cancer, Expert Rev Anticancer Ther. 17 (5) (2017) 399–409.
[99] C.K. Lee, J. Man, S. Lord, W. Cooper, M. Links, V. Gebski, R.S. Herbst, R.J. Gralla, T. Mok, J.-H. Yang, Clinical and molecular characteristics associated with survival among patients treated with checkpoint inhibitors for advanced non-small cell lung carcinoma: A systematic review and meta-analysis, JAMA Oncol. 4 (2) (2018) 210.
[100] A. Lisberg, A. Cummings, J.W. Goldman, K. Bornazyan, N. Reese, T. Wang, P. Coluzzi, B. Ledezma, M. Mendenhall, J. Hunt, B. Wolf, B. Jones, J. Madrigal, J. Horton, M. Spiegel, J. Carroll, J. Gukasyan, T. Williams, L. Sauer, C. Wells, A. Hardy, P. Linares, C. Lim, L. Ma, C. Adame, E.B. Garon, A Phase II Study of Pembrolizumab in EGFR-Mutant, PD-L1+, Tyrosine Kinase Inhibitor Naïve Patients With Advanced NSCLC, J Thorac Oncol. 13 (8) (2018) 1138–1145.
[101] P. Christopoulos, K. Kluck, M. Kirchner, H. Lüders, J. Roeper, R.-F. Falkenstern-Ge, M. Szewczyk, F. Sticht, F.C. Saalfeld, C. Wesseler, B. Hackanson, S. Dintner, M. Faehling, J. Kuon, M. Janning, D. Kauffmann-Guerrero, D. Kazdal, S. Kurz, F. Eichhorn, F. Bozorgmehr, R. Shah, A. Tufman, M. Wermke, S. Loges, W. M. Brueckl, C. Schulz, D. Misch, N. Frost, J. Kollmeier, M. Reck, F. Griesinger, C. Grohé, J.-L. Hong, H.M. Lin, J. Budczies, A. Stenzinger, M. Thomas, The impact

of TP53 co-mutations and immunologic microenvironment on outcome of lung cancer with EGFR exon 20 insertions, Eur J Cancer. 170 (2022) 106–118.
[102] Z.-R. Zhao, Y.-B. Lin, C.S.H. Ng, R. Zhang, X. Wu, Q. Ou, W. Chen, W.-J. Zhou, Y.-B. Lin, X.-D. Su, Y.W. Shao, H. Long, Mutation Profile of Resected EGFR -Mutated Lung Adenocarcinoma by Next-Generation Sequencing, Oncologist. 24 (10) (2019) 1368–1374.
[103] F. Le Calvez, A. Mukeria, J.D. Hunt, O. Kelm, R.J. Hung, P. Tanière, P. Brennan, P. Boffetta, D.G. Zaridze, P. Hainaut, TP53 and KRAS mutation load and types in lung cancers in relation to tobacco smoke: distinct patterns in never, former, and current smokers, Cancer Res. 65 (12) (2005) 5076–5083.
[104] R. Jin, L. Peng, J. Shou, J. Wang, Y. Jin, F. Liang, J. Zhao, M. Wu, Q. Li, B. Zhang, X. Wu, F. Lan, L. Xia, J. Yan, Y. Shao, J. Stebbing, H. Shen, W. Li, Y. Xia, EGFR-Mutated Squamous Cell Lung Cancer and Its Association With Outcomes, *Front Oncol.* 11 (2021), https://doi.org/10.3389/fonc.2021.680804.
[105] R. Jin, J. Zhao, L. Xia, Q. Li, W. Li, L. Peng, Y. Xia, Application of immune checkpoint inhibitors in EGFR-mutant non-small-cell lung cancer: from bed to bench, Ther Adv, Med Oncol. 9 (12) (2020), 175883592093033, https://doi.org/10.1177/1758835920930333.
[106] M.A. Curran, Preclinical Data Supporting Antitumor Activity of PD-1 Blockade, Cancer J 24 (1) (2018) 2–6.
[107] N. Chen, W. Fang, J. Zhan, S. Hong, Y. Tang, S. Kang, Y. Zhang, X. He, T. Zhou, T. Qin, Y. Huang, X. Yi, L.i. Zhang, Upregulation of PD-L1 by EGFR activation mediates the immune escape in EGFR-driven NSCLC: Implication for optional immune targeted therapy for NSCLC patients with EGFR mutation, J Thorac Oncol. 10 (6) (2015) 910–923.
[108] Y. Jin, Q. Xue, X. Shen, Q. Zheng, H. Chen, X. Zhou, Y. Li, PD-L1 Expression and Comprehensive Molecular Profiling Predict Survival in Nonsmall Cell Lung Cancer: A Real-World Study of a Large Chinese Cohort, Clin Lung Cancer. 23 (1) (2022) 43–51.
[109] F. Skoulidis, M.E. Goldberg, D.M. Greenawalt, M.D. Hellmann, M.M. Awad, J. F. Gainor, A.B. Schrock, R.J. Hartmaier, S.E. Trabucco, L. Gay, S.M. Ali, J. A. Elvin, G. Singal, J.S. Ross, D. Fabrizio, P.M. Szabo, H. Chang, A. Sasson, S. Srinivasan, S. Kirov, J. Szustakowski, P. Vitazka, R. Edwards, J.A. Bufill, N. Sharma, S.I. Ou, N. Peled, D.R. Spigel, H. Rizvi, E.L. Aguilar, B.W. Carter, J. Erasmus, D.F. Halpenny, A.J. Plodkowski, N.M. Long, M. Nishino, W. L. Denning, A. Galan-Cobo, H. Hamdi, T. Hirz, P. Tong, J. Wang, J. Rodriguez-Canales, P.A. Villalobos, E.R. Parra, N. Kalhor, L.M. Sholl, J.L. Sauter, A. A. Jungbluth, M. Mino-Kenudson, R. Azimi, Y.Y. Elamin, J. Zhang, G.C. Leonardi, F. Jiang, K.K. Wong, J.J. Lee, V.A. Papadimitrakopoulou, I.I. Wistuba, V.A. Miller, G.M. Frampton, J.D. Wolchok, A.T. Shaw, P.A. Jänne, P.J. Stephens, C.M. Rudin, W.J. Geese, L.A. Albacker, J.V. Heymach, *STK11/LKB1* Mutations and PD-1 Inhibitor Resistance in *KRAS*-Mutant Lung Adenocarcinoma, Cancer Discov. 8 (7) (2018) 822–835.
[110] D. Marinelli, M. Mazzotta, S. Scalera, I. Terrenato, F. Sperati, L. D'Ambrosio, M. Pallocca, G. Corleone, E. Krasniqi, L. Pizzuti, M. Barba, S. Carpano, P. Vici, M. Filetti, R. Giusti, A. Vecchione, M. Occhipinti, A. Gelibter, A. Botticelli, F. De Nicola, L. Ciuffreda, F. Goeman, E. Gallo, P. Visca, E. Pescarmona, M. Fanciulli, R. De Maria, P. Marchetti, G. Ciliberto, M. Maugeri-Saccà, KEAP1-driven co-mutations in lung adenocarcinoma unresponsive to immunotherapy despite high tumor mutational burden, Ann Oncol. 31 (12) (2020) 1746–1754.
[111] K.C. Arbour, E. Jordan, H.R. Kim, J. Dienstag, H.A. Yu, F. Sanchez-Vega, P. Lito, M. Berger, D.B. Solit, M. Hellmann, M.G. Kris, C.M. Rudin, A. Ni, M. Arcila, M. Ladanyi, Effects of Co-occurring Genomic Alterations on Outcomes in Patients with *KRAS*-Mutant Non-Small Cell Lung Cancer, Clin Cancer Res 24 (2) (2018) 334–340.
[112] S. Scalera, M. Mazzotta, G. Corleone, F. Sperati, I. Terrenato, E. Krasniqi, L. Pizzuti, M. Barba, P. Vici, E. Gallo, S. Buglioni, P. Visca, E. Pescarmona, D. Marinelli, F. De Nicola, L. Ciuffreda, F. Goeman, M. Fanciulli, R. Giusti, A. Vecchione, R. De Maria, F. Cappuzzo, P. Marchetti, G. Ciliberto, M. Maugeri-Saccà, KEAP1 and TP53 Frame Genomic, Evolutionary, and Immunologic Subtypes of Lung Adenocarcinoma With Different Sensitivity to Immunotherapy, J Thorac Oncol. 16 (12) (2021) 2065–2077.
[113] W.-K. Choong, T.-Y. Sung, Somatic mutation subtypes of lung adenocarcinoma in East Asian reveal divergent biological characteristics and therapeutic vulnerabilities, iScience 24 (6) (2021) 102522.
[114] K. Chen, G. Pan, G. Cheng, F. Zhang, Y. Xu, Z. Huang, Y. Fan, Immune microenvironment features and efficacy of PD-1/PD-L1 blockade in non-small cell lung cancer patients with EGFR or HER2 exon 20 insertions, Thorac Cancer. 12 (2) (2021) 218–226.
[115] J. Hu, J. Cao, W. Topatana, S. Juengpanich, S. Li, B. Zhang, J. Shen, L. Cai, X. Cai, M. Chen, Targeting mutant p53 for cancer therapy: direct and indirect strategies, J Hematol Oncol. 14 (1) (2021), https://doi.org/10.1186/s13045-021-01169-0.
[116] C. Yang, G. Lou, W.L. Jin, The arsenal of TP53 mutants therapies: neoantigens and bispecific antibodies, *Signal Transduct Target Ther.* (2021), https://doi.org/10.1038/s41392-021-00635-y.
[117] H. Song, J. Wu, Y. Tang, Y. Dai, X. Xiang, Y.a. Li, L. Wu, J. Wu, Y. Liang, Y. Xing, N.i. Yan, Y. Li, Z. Wang, S. Xiao, J. Li, D. Zheng, X. Chen, H. Fang, C. Ye, Y. Ma, Y. u. Wu, W. Wu, J. Li, S. Zhang, M. Lu, Diverse rescue potencies of p53 mutations to ATO are predetermined by intrinsic mutational properties, Sci Transl Med. 15 (690) (2023), https://doi.org/10.1126/scitranslmed.abn9155.
[118] S. Shang, F. Hua, Z.-W. Hu, The regulation of β-catenin activity and function in cancer: Therapeutic opportunities, Oncotarget. 8 (20) (2017) 33972–33989.
[119] V. Thomas de Montpréville, L. Lacroix, E. Rouleau, M. Mamodaly, J. Leclerc, L. Tutuianu, D. Planchard, D. Boulate, O. Mercier, B. Besse, É. Fadel, M.-R. Ghigna, Non-small cell lung carcinomas with CTNNB1 (beta-catenin) mutations: A clinicopathological study of 26 cases, Ann Diagn Pathol. 46 (2020) 151522.
[120] K.G. Wiman, The retinoblastoma gene: role in cell cycle control and cell differentiation, FASEB J. 7 (10) (1993) 841–845.
[121] J. Füllgrabe, E. Kavanagh, B. Joseph, Histone onco-modifications, Oncogene 30 (31) (2011) 3391–3403.
[122] K. Lai, M.C. Killingsworth, C.S. Lee, Gene of the month: PIK3CA, J Clin Pathol. 68 (4) (2015) 253–257.
[123] Z. Zhang, A. Richmond, The Role of PI3K Inhibition in the Treatment of Breast Cancer, Alone or Combined With Immune Checkpoint Inhibitors, Front Mol Biosci. (2021), https://doi.org/10.3389/fmolb.2021.648663.
[124] X. Qiu, Y. Wang, F. Liu, L. Peng, C. Fang, X. Qian, X. Zhang, Q. Wang, Z. Xiao, R. Chen, S. Yuan, Survival and prognosis analyses of concurrent PIK3CA mutations in EGFR mutant non-small cell lung cancer treated with EGFR tyrosine kinase inhibitors, Am J Cancer Res 11 (6) (2021) 3189–3200.
[125] S. Scalera, M. Mazzotta, C. Cortile, E. Krasniqi, R. De Maria, F. Cappuzzo, G. Ciliberto, M. Maugeri-Saccà, KEAP1-Mutant NSCLC: The Catastrophic Failure of a Cell-Protecting Hub, J Thorac Oncol. 17 (6) (2022) 751–757.
[126] S.A. Best, K.D. Sutherland, "Keaping" a lid on lung cancer: the Keap1-Nrf2 pathway, Cell Cycle. 17 (14) (2018) 1696–1707.
[127] K.B. Emdal, A. Dittmann, R.J. Reddy, R.S. Lescarbeau, S.L. Moores, S. Laquerre, Characterization of *In Vivo* Resistance to Osimertinib and JNJ-61186372, an EGFR/Met Bispecific Antibody, Reveals Unique and Consensus Mechanisms of Resistance, Mol Cancer Ther 16 (11) (2017) 2572–2585.
[128] M.M. Saleh, M. Scheffler, S. Merkelbach-Bruse, A.H. Scheel, B. Ulmer, J. Wolf, R. Buettner, Comprehensive Analysis of TP53 and KEAP1 Mutations and Their Impact on Survival in Localized- and Advanced-Stage NSCLC, J Thorac Oncol. 17 (1) (2022) 76–88.
[129] Zavitsanou A-M, Hao Y, Wu WL, et al. KEAP1 mutation in lung adenocarcinoma promotes immune evasion and immunotherapy resistance. *bioRxiv*. 2021: 2021.09.24.461709. https://www.biorxiv.org/content/10.1101/2021.09.24.461709v1%0Ahttps://www.biorxiv.org/content/10.1101/2021.09.24.461709v1.abstract.
[130] Y. Bao, S. Zhang, X. Zhang, Y. Pan, Y. Yan, N. Wang, Y. Ren, J. Zuo, W.X. Zong, Z. Wang, Y. Wang, RBM10 Loss Promotes EGFR-Driven Lung Cancer and Confers Sensitivity to Spliceosome Inhibition, Cancer Res. 83 (9) (2023) 1490–1502.
[131] S. Nanjo, W. Wu, N. Karachaliou, C.M. Blakely, J. Suzuki, Y.-T. Chou, S.M. Ali, D. L. Kerr, V.R. Olivas, J. Shue, J. Rotow, M.K. Mayekar, F. Haderk, N. Chatterjee, A. Urisman, J.C. Yeo, A.J. Skanderup, A.C. Tan, W.L. Tam, O. Arrieta, K. Hosomichi, A. Nishiyama, S. Yano, Y. Kirichok, D.S.W. Tan, R. Rosell, R. A. Okimoto, T.G. Bivona, Deficiency of the splicing factor RBM10 limits EGFR inhibitor response in EGFR-mutant lung cancer, J Clin Invest. 132 (13) (2022), https://doi.org/10.1172/JCI145099.
[132] V. Gristina, M. La Mantia, A. Galvano, S. Cutaia, N. Barraco, M. Castiglia, A. Perez, M. Bono, F. Iacono, M. Greco, K. Calcara, V. Calò, S. Rizzo, L. Incorvaia, M.C. Lisanti, G. Santanelli, D. Sardo, S. Inguglia, L. Insalaco, L. Castellana, S. Cusenza, G. Pantuso, A. Russo, V. Bazan, Non-Small Cell Lung Cancer Harboring Concurrent EGFR Genomic Alterations: a Systematic Review and Critical Appraisal of the Double Dilemma, J Mol Pathol. 2 (2) (2021) 173–196.
[133] Z. Tang, J. Zhang, X. Lu, W. Wang, H. Chen, M.K. Robinson, J. Cheng, G. Tang, L. J. Medeiros, Coexistent genetic alterations involving ALK, RET, ROS1 or MET in 15 cases of lung adenocarcinoma, Mod Pathol. 31 (2) (2018) 307–312.