Introduction

Lung cancer represents the main cause of death by cancer worldwide [1]. The global five-year survival rate of lung cancer is only 16%, mostly because of the high frequency of delayed diagnosis, with non-resectable tumors [1]. Lung cancer can be classified in four major categories: pulmonary adenocarcinoma, squamous-cell carcinoma, large-cell carcinoma, which forms non-small cell lung cancer (NSCLC), and small cell lung carcinoma [2].

The low survival rate of lung cancer reflects the scarcity of traditional cytotoxic chemotherapy; specific treatments oriented towards certain weak spots of the tumor cells are the most important promise for the future. Somatic mutations that activate oncogenes frequently lead to the addiction of tumor cells towards modified oncogene products [3,4], a property that targeted therapy can exploit.
therapy exploits. Therefore, identifying the recurrent oncogenic lesions of which the survival of tumor cells depends on may lead to novel therapies in lung cancer.

A wide scale experiment of direct sequencing of tumor exome, the Project of Tumor Sequencing (PTS) has been performed in order to determine recurrent somatic mutations in pulmonary adenocarcinoma. Within this experiment, all coding exons of 623 genes with a role in oncogenesis have been sequenced in 188 pairs of normal tissue / tumor DNA, which led to the identification of 1013 non-synonym somatic mutations [5]. The statistical analysis has indicated 26 genes with significant mutations.

These 26 genes with significant mutations have included more oncogenes and suppressor genes that are already known to be involved in lung cancer: KRAS, TP53, STK11, EGFR and CDKN2A. Other genes with significant mutations have also been identified, unidentified up to that point in pulmonary adenocarcinoma, including several known suppressor genes and a few tyrosine kinase genes, whose functional validation is ongoing.

We describe the up-to-date knowledge regarding lung cancer genome, emphasizing the therapeutical implications.

The future knowledge arisen from sequencing the entire exome and the entire genome, enabled by novel sequencing technologies, will most likely revolutionize once again the understanding of this disease’s genome.

Gene mutations

Exclusive mutations

The somatic alterations of 7 oncogenes in lung cancer [6]: KRAS, EGFR, ALK, ERBB2, BRAF HER2 and ROS1 balance each other out. Five of these genes (KRAS, EGFR, ALK, ERBB2, BRAF) are found in more than 50% of the pulmonary adenocarcinomas. In fact, the patients with mutations in these five genes can represent up to 90% of Asian patients that have never smoked [7]. Therefore, the possibility to therapeutically inhibit the functions of these modified genes would represent a significant progress in the fight against lung cancer.

**KRAS**

Three different RAS genes have been identified in humans: KRAS (homologue with Kirsten sarcoma virus oncogene in rats), HRAS (homologue with Harvey sarcoma virus oncogene in rats) and NRAS (initially isolated in a human neuroblastoma). RAS has been involved in the pathogenesis of several types of cancer. Mutational activation of RAS gene results in the constitutive activation of RAS GTPase, even in the absence of signaling by growth factors. The result is a continuous signal of cell proliferation. KRAS mutations are very frequent in colon cancer, lung cancer and pancreatic cancer [8]. RAS genes are structurally very similar, but different from a functional point of view. RAS proteins are small GTPase, which switch from inactive-related guanosine diphosphate (GDP) forms to active-related guanosine triphosphate (GTP) forms. RAS proteins are downstream key mediators towards growth factor receptors and are essential for the proliferation, survival and cell differentiation. RAS has the capacity to downstream activate signaling pathways within the cell. These pathways include PI3K - AKT – mTOR pathway, which is involved in cell survival, and RAS - RAF - MEK – ERK pathway, which is involved in cell proliferation.

Approximately 15-25% of pulmonary adenocarcinoma patients have KRAS mutations. In most cases, these mutations are non-sense mutations results by replacing an amino acid on position 12 (least frequent), 13 or 61. This leads to the constitutive activation of KRAS signaling pathways. KRAS mutations are rare in squamous cell carcinoma [9].

KRAS mutations are found in tumors both in smokers and in former smokers, as well as in non-smokers. They are rather infrequent in non-smokers and in Asian patients, compared to North-Americans or Europeans [7, 10, 11].

KRAS does not seem to present a prognosis value in untreated NSCLC [12] but KRAS mutations are a negative predictor factor of the radiologic response to EGFR tyrosine kinase inhibitors [10, 13]. In a study that has included 17 patients with KRAS mutations, ganetespib, a HSP90 inhibitor, has shown a reduced activity [14]. In humans, selumetinib, a MEK1/MEK2 inhibitor, in association with docetaxel, has proven an activity in patients that were in second-phase treatment for metastatic NSCLC with mutant KRAS. In this randomized study, the relapse-free period (RFP) was 5.3 months in selumetinib / docetaxel groups versus 2.1 months in placebo / docetaxel group (HR 0.58 p = 0.014) [15].

Currently, there is no drug with anti-KRAS direct effect.
**EGFR**

The epidermal growth factor receptor (EGFR) belongs to a family of receptors tyrosine kinase (RTK), which include EGFR/ERBB1, HER2/ERBB2/NEU, HER3/ERBB3 and HER4/ERBB4. Ligand binding, such as epidermal growth factor (EGF), induces a conformational alteration that allows homo or hetero dimerization of the receptor. Thus activated, EGFR phosphorylates its sublayers, leading to the activation of various downstream signaling pathways in the cell: PI3K-AKT-mTOR, involved in cell survival and RAS-RAF-MEK-ERK, involved in cell proliferation.

Approximately 10% of the patients with NSCLC in the US and 35% in East Asia display EGFR in tumors [16]. EGFR mutations are far more frequent in adenocarcinomas in female non-smokers (defined as less than 100 cigarettes smoked throughout the patient’s life). EGFR mutations can also be found in other NSCLC subgroups: current smokers and former smokers, other histological types. These mutations are produced in exons 18 and 21 of the EGFR gene, which codifies a section in the kinase domain of the receptor. Approximately 90% of these mutations are deletions in exon 19 or L858R punctual mutations in exon 21 [17]. These mutations determine the activity increase of EGFR kinase, which leads to a downstream signaling pathway hyperactivation [18] and a sensitivity to treatment with tyrosine kinase inhibitors. Nevertheless, these mutations (insertions in exon 20, mutation T790M) signal the presence of an initial resistance or, more frequently, acquired resistance to tyrosine kinase inhibitors [19].

**ALK**

ALK is a tyrosine kinase receptor that can be abnormal in various types of cancer. For instance, activation mutation of ALK is found in some neuroblastomas [20]. ALK fusions have been described in large-cell anaplastic lymphoma (NPM-ALK) [21], in inflammatory myofibroblast tumors (IMT) [22] and in non-small cell lung cancer (NSCLC) [23-25]. All ALK fusions contain the entire tyrosine kinase domain of the receptor. Up to the present, all biologically evaluated ALK fusions have proven an in vitro and in vivo oncogenic activity [21, 24, 25].

Different N-terminal fusion partners favor dimerization and thus the kinase activity [26]. The downstream signaling of these fusions translates into the activation of the pathways involved in cell proliferation and growth.

ALK gene fusions are present in approximately 3-7% of the pulmonary tumors [24, 27, 28]. Their presence has proven the efficacy of the first ALK inhibitor, crizotinib. These ALK fusions are especially found in small quantity smokers (<10 PA) and / or non-smokers [24, 27-29]. ALK fusions are also more frequent in young patients’ tumors [27-29] in acinar adenocarcinomas [28, 29] or present in seal ring cells [27].

Therapeutically, the presence of EML4-ALK’s fusion is associated with EGFR (EGFR TKI) inhibitor resistance [30]. Various types of ALK-rearranged have been described in NSCLC. Most of these fusion versions comprise a part of the EML4 gene associated with ALK gene. At least nine versions of EML4-ALK fusion have been identified in NSCLC [24, 25, 28]. In addition, non-AML4 fusion versions have been identified, for instance KIF5B-ALK [25] and TFG-ALK [23]. In most cases, ALK-rearranged excludes the presence of other oncogenic mutations in NSCLC (EGFR mutations, KRAS mutations etc.) [27, 28, 29, 31]. Even so, the co-existence with other molecular aberrations (EGFR and especially MET mutations) has been described [32].

Crizotinib (Xalkori), a c-MET receptor and ALK inhibitor, has been recently approved by the American and European authorities in the NSCLC treatment for patients with ALK fusions [33].

In a phase I study involving 149 patients with ALK fusion, the radiologic response rate has been of 61% for crizotinib treatment, a ALK / MET inhibitor (TKI) [34]. The median progression-free survival has been of 9.7 months and 75% of the patients were alive after one year. An international phase III randomized study, in advanced lung cancer presenting ALK fusions, compared crizotinib with standard chemotherapy as treatment after the disease progression, subsequent to standard treatment previously applied. The results show a benefit for crizotinib in terms of progression-free survival: 7.7 months vs. 3.0 months for standard chemotherapy [35]. New ALK inhibitors are currently being developed, such as CH5424802, with a response rate of 93.5% in a phase II study in patients who have not been previously treated with ALK inhibitor [36].

Up to now, several punctiform mutations in ALK tyrosine kinase domain have been found in patients with acquired resistance to crizotinib, TKI ALK inhibitor.

Currently, the mechanisms of acquired resistance to crizotinib, an ALK / MET inhibitor, are not well
known. Several studies on small cohorts of patients have shown that mutations in ALK kinase domain can lead to acquired resistance to crizotinib. The described mutations can confer different degrees of sensibility or resistance to second generation ALT TKI.

New therapeutic strategies are presently evaluated in patients with NSCLC ALK+, in order to treat or to prevent the resistance associated to this mutation [37].

**ERBB2**

Somatic mutations of ERBB2 in pulmonary adenocarcinoma have been described for the first time the same year the EGFR mutations have, although at a lower frequency, of approximately 2-4% [38]. These mutations are small insertions in the kinase domain of exon 20, analogue to the primary resistance mutations of EGFR in paralogue exon 20. ERBB2 is a tyrosine kinase receptor that does not bind any known ligand, but homodimerizes or heterodimerizes with EGFR and other members of ERBB, ERBB3 and ERBB4 family, in order to activate the downstream signaling pathways [39]. These activation mutations respond in vitro to irreversible EGFR inhibitors, which also bind and inhibit ERBB2 [40, 41]. Trastuzumab antibody is active in undetermined breast cancer for amplified ERBB2; it is not promising in preclinical models with mutant ERBB2 [41].

Oncogenic mutations sensible to drugs of EGFR extracellular domain have been described in glioblastoma [42], which suggests the possibility that mutations of the ERBB2 extracellular domain to be also found in cancer patients. In fact, the existence of S310F mutation has been reported in pulmonary adenocarcinoma, coding ERBB2 mutation.

**BRAF**

BRAF mutations have been involved in the pathogenesis of various types of cancer, including melanoma, non-small cell lung cancer, colorectal cancer, thyroid papillary cancer and ovarian cancer [43].

BRAF is a kinase that plays a key role in the signaling pathway of MAP kinase, and belongs to a serine-threonine kinase family that includes ARAF, BRAF and CRAF (RAF1). RAF kinases are key mediators in the signaling pathway of MAP kinase. They carry out their effect mainly by phosphorylating and activating MEK, which takes place by dimerization (homo or hetero) of RAF molecules. As part of MAP kinase pathway, RAF plays an essential part in many cellular processes, such as proliferation, differentiation and transcriptional regulation.

BRAF somatic mutations have been found in approximately 3-5% of NSCLC [9, 43, 44], mainly in adenocarcinomas. BRAF mutations are mainly found in smokers or former smokers [45].

Most BRAF mutations appear in valine 600 (mutation V600) in exon 15 of kinase domain, but also occur on other levels of the kinase domain. In a study on 739 patients with pulmonary adenocarcinoma, 36 patients displayed BRAF mutations (4.9%). In these 36 patients, the identified BRAF mutations were V600E type in 57% of the cases and non-V600E in 43% of the cases [44]. In another series, a 50% V600E and 50% non-V600E ratio has been found [46].

**HER2**

HER2 belongs to a family of receptors tyrosine kinase (RTKs), which include EGFR/ERBB1, HER2/ERBB2/NEU, HER3/ERBB3 and HER4/ERBB4. HER2 gene is localized on chromosome 17; this is amplified with several copies of the gene in different types of cancer [47].

No HER2 ligands are currently known. However, HER2 seem to be the favorite dimerization partner for all ERBB family receptors [48]. Ligand binding, followed by the heterodimerization of the receptor determines HER2 kinase activation. Activated HER2 phosphorylates its layers, leading to the activation of several downstream signaling pathways within the cell. These pathways include PI3K - AKT - mTOR, which is involved in cell survival and RAS - RAF - MEK – ERK pathway, involved in cell proliferation.

HER2 mutations are rare in lung cancer (2-4% of NSCLC) [38]. The most frequent mutation is an insertion in exon 20 [65]. HER2 mutations are more frequent in non-smokers (defined as less than 100 cigarettes smoked throughout the patient’s life) and in adenocarcinoma [38 49]. However, HER2 mutations can be found in other NSCLC subtypes, including in smokers or former smokers or in other histological types [38]. Insertions in exon 20 determine a hyperactivity of kinase HER2, followed by the activation of downstream signaling pathway; this results in the increase of cell survival, invasion and tumor development [41].

HER2 amplification is not a prognosis factor in NSCLC. Preliminary results suggest the efficacy of some anti-HER2 therapies.
ROS1

ROS1 is a receptor tyrosine kinase (RTK), belonging to the insulin receptors family. Chromosomal rearrangements involving ROS1 gene, on 6q22 chromosome, have been initially described in glioblastoma (for instance, FIG – ROS1) [50, 51]. More recently, fusions of ROS1 have been identified as causal aberrations in non-small cell lung cancer [23]. ROS1 fusions incorporate an intact tyrosine kinase domain. Biologically, the fusions that have been studied display oncogenic activity [23, 51]. Downstream ROS1 fusions, the signaling activates the known cellular pathways as involved in cell growth and proliferation. In vitro, ROS1 fusions are associated with sensitivity to inhibitors of active ROS1 tyrosine kinase [52].

ROS1 fusions have been found in approximately 2% of the lung cancer cases [53] and are more frequent in light smokers (< 10 packs years) and / or non-smokers. Several ROS1-rearranged have been found in NSCLC. These include SLC34A2 - ROS1 and CD74 - ROS1. ROS1 fusions are especially associated with young ages and adenocarcinoma histology [53]. Two Asian series have reported 31 cases of ROS1 fusions: all of the cases proved to be adenocarcinoma [54, 55]. In preclinical models, ROS1 fusions show a sensitivity to tyrosine kinase inhibitors that present a collateral activity on ROS1, such as crizotinib [53]. Preliminary results indicate the efficacy of crizotinib, a ALK / MET inhibitor, acting on ROS1 (53, 56).

Non-exclusive mutations

DDR2

DDR (Discoidin Death Receptor 2) is a member of the family of DDR tyrosine kinase receptors, which are stimulated by collagen, not by peptide growth factors. Downstream signaling in cancer cells in not well known, but it could be made by SRC and STAT signaling pathways. As well as the integrin receptors, DDR2 can play a role by modulating cellular interaction with extracellular matrix.

DDR2 mutations have been found in several types of cancer, including renal-cell carcinoma, multiforme glioblastoma, endometrial cancer, colorectal cancer (Catalogue of Somatic Mutations in Cancer - COSMIC). It is most frequent in squamous-cell pulmonary carcinoma [57].

DDR2 mutations have been found in 3.8% in squamous-cell lung carcinomas, but in less than 1% of the non-squamous lung tumors [COSMIC; 57]. No specific location has been identified, the mutations being in the discoidin and kinase domain. No significant association with gender, age or smoking has been found.

FGFR1

The gene of fibroblast growth factors receptor type 1 (FGFR1) codifies one of the subtypes of tyrosine kinase (TK) FGFR receptors family. There are four such families: FGFR1, 2, 3 and 4. FGFR TK play a key role in the development and are generally dysregulated in cancer, by amplification, punctual mutations or translocations [58]. Amplification or aleactivation of FGFR1 has been described in various types of cancer, including squamous-cell mouth cancer [86], breast cancer [59], squamous-cell esophageal carcinoma [60], ovarian cancer [61], urinary bladder cancer [62], prostate cancer [63] and lung cancer, especially squamous-cell type [64].

FGFR1 amplifications are frequent, found in approximately 20% of squamous-cell lung cancer and smoking-related. In Asian patients, FGFR1 amplification is related to tobacco use importance; it also constitutes an independent factor of poor prognosis [65]. In patients suffering from other histological types of lung cancer, such as adenocarcinoma, FGFR1 amplifications are not so frequent (less than 2%) [65]. Preclinical data suggest that cancer cells that present a FGFR1 amplification are FGFR signaling pathway dependent. FGFR inhibitors are currently being developed.

MET

MET gene (MNNG – HOS transforming gene [66]), localized on chromosome 7, codifies for a tyrosine kinase receptor (RTK) belonging to the MET / RON. Ligand binding, hepatocyte growth factor (HGF, also known as scatter factor (SF)), produces a conformational change of the MET receptor, which induces phosphorylation and receptor activation. Activated MET phosphorylates its sublayers, leading to the downstream activation of several signaling pathways. These pathways include PI3K - AKT – mTOR pathway, which is involved in cell survival and RAS - RAF - MEK – ERK pathway, involved in cell proliferation. In cancer, MET receptor abnormal signaling induces reactions to the metastasis process [67].

It has been shown that the MET receptor and its
HGF ligand have been abnormally activated in various human cancers. Germinal mutations in MET tyrosine kinase domain are found in 100% of hereditary papillary renal cancer cases and MET somatic mutations are present in 10-15% of the sporadic renal papillary carcinoma [68]. MET mutations have been found with a lower frequency in squamous-cell head and neck cancers [69], in hepatocellular child’s carcinoma [70], in NSCLC [71, 72] and in small-cell lung cancer [72]. MET amplifications have been described in gastric cancer [73], in esophageal cancer [74], in colorectal cancer [75], in gliomas [76], in clear-cell ovarian cancer [77] and in NSCLC [78].

MET activation mechanisms have been described in NSCLC, including mutations [71, 72] and gene amplification [78]. MET aberrations found in lung cancer mainly consisted in a gene amplification, especially in patients with EGFR mutations and tyrosine kinase inhibitor resistant.

MET inhibitor activity in NSCLC and in small-cell lung cancer is not known for the tumors with mutations outside kinase domain. However, foretinib responses have been reported (XL880 or GSK136308), a MET and other tyrosine kinase inhibitor, including VEGFR2, active on oral path, in patients with papillary renal-cell carcinoma [79].

An overexpression of the tumor tissue protein compared to adjacent normal tissue is present in 25-75% of NSCLC and it represents a poor prognosis factor [80]. In a phase II study, NSCLC patients have been randomized between MetMAb (anti-MET antibodies) in association with erlotinib, as opposed to erlotinib alone. The overexpression of MET protein has been associated with an increase of progression-free survival and global survival in patients treated with MetMAb and erlotinib [81].

**NRAS**

In humans, three different RAS genes have been identified: KRAS (homologue with Kirsten sarcoma virus oncogene in rats), HRAS (homologue with Harvey sarcoma virus oncogene in rats) and NRAS (initially isolated in a human neuroblastoma). The RAS genes are homologue, but functionally different. RAS proteins are small GTPase, which switch from inactive-related guanosine diphosphate (GDB) forms to active-related guanosine triphosphate (GTP) forms. RAS proteins are downstream key mediators towards growth factor receptors and are essential for the proliferation, survival and cell differentiation. RAS has the capacity to downstream activate signaling pathways within the cell. These pathways include PI3K - AKT – mTOR pathway, which is involved in cell survival, and RAS - RAF - MEK – ERK pathway, which is involved in cell proliferation.

Mutational activation of RAS gene results in the constitutive activation of RAS GTPase, even in the absence of signaling by growth factors. The result is a continuous signal of cell proliferation. RAS specific genes are frequently mutated in different types of cancer. NRAS mutations are very frequent in colon cancer, melanoma, hepatocellular carcinoma, myeloid leukemia and thyroid cancer [82].

Approximately 1% of non-small cell lung cancer patients display NRAS mutations. NRAS mutations are rare in squamous-cell carcinoma and in non-smokers [9, 5, 83]. In most cases, these mutations are non-sense mutation by switching the amino acid on position 12 and 61. This leads to the constitutive activation of NRAS signaling pathways. In most cases, NRAS mutations are exclusive to other oncoprotein mutations found in NSCLC (such as EGFR mutations, ALK-rearranged etc.).

Currently, there is no anti-NRAS targeted therapy, but preclinical studies suggest that MEK inhibitors (selumetinib, trametinib) might be active [83].

**PIK3CA**

Phosphatidyl 3-kinases (PI3K) represent a lipid kinase family involved in numerous cell processes, such as growth, proliferation, differentiation, mobility and survival. PI3K is a two-subunit heterodimer: an 85 kDa (p85) regulation subunit and a 110 kDa catalytic subunit. PIK3CA gene codifies p110α, one of the catalytic subunits.

PI3K converts PI (4,5) P2 [phosphatidylinositol 4,5 bisphosphate] into PI (3, 4, 5) P3 [phosphatidylinositol (3, 4, 5) triphosphate] within the internal leaf of the cell membrane. PI (3, 4, 5) P3 activates on the important membrane level signaling proteins, such as AKT, leading to the increase of these proteins activity.

Mutant PIK3CA is involved in the pathogenesis of many types of cancer, such as gliomas, colon, stomach, breast, endometrial and lung cancer [COSMIC: 84].

PIK3CA somatic mutations have been found in 1-3% of all NSCLC; they seem to be more frequent in squamous-cell cancer cases and have been found in
both smokers and non-smokers [COSMIC; 84, 85]. These changes generally occur on two critical points of exon 9 (helical domain) and exon 20 (kinase domain). PIK3CA mutations can co-exist with EGFR mutations [7, 85]. Moreover, PIK3CA mutations (~5%) have been detected in EGFR mutations lung cancer, displaying an acquired resistance to EGFR tyrosine kinase inhibitors [86]. Presently, PIK3 and PIK3/mTOR inhibitors are being clinically developed.

RET

RET gene (‘rearranged during transfection’) [87], is localized on chromosome 10; this codifies a receptor tyrosine kinase (RTK) belonging to the RET family. Ligand binding belonging to the glial cell line derived neurotrophic factor (GDNF) family induces phosphorylation and receptor activation; these ligands are extracellular signaling molecules [88]. Once it has been activated, RET phosphorylates its sublayers, determining downstream activation of the signaling pathways [89].

RET aberrations can be found especially in thyroid cancer. Punctual and germinal somatic mutations are found in medullary thyroid cancer [90]. RET fusions are also found in some pulmonary adenocarcinoma [91].

Approximately 1.3% of the pulmonary tumors, usually adenocarcinomas, present chromosomal alterations, such as RET fusion genes [92, 93]. The most frequent fusion genes are CCDC6-RET and KIF5B-RET and NCOA4-RET [93].

The functional consequences of the RET fusion proteins in pulmonary adenocarcinoma are not fully understood; however, it is known that they are oncogenic in vitro and in vivo. At in vitro models, RET fusion products can be sensible to multi-target kinase inhibitors, such as vandetanib, sorafenib, sunitinib and cabozantinib [93, 94]. Clinically, there are still few prospective data allowing for a connection to be made between the RET fusions and the response to certain treatments [95]. Several studies explore the activity of RET tyrosine kinase inhibitors.

Conclusion

The sequencing of lung cancer exon has allowed the understanding of oncogenesis mechanisms.

Several factors influence these experiments, including the loss of power in the detection of specific tumoral somatic mutations in the stromal contamination, as well as a limited capacity to detect mutations in a codification sequence subset. The decrease in the sequencing cost has allowed the recent launch of sequencing projects of the entire exome and of the entire genome of lung cancer, which allows an analysis of the mutations in an impartial manner. Moreover, data gathering by next-generation sequencing methods is “digital”, realized for each cell; therefore, the capacity to detect low abundance allele only depends on the covering capacity, either because of stromal contamination or due to the heterogeneity of the tumor. Generating sequencing data of the entire exome and of the entire genome from an increasingly higher number of samples will allow a global insight of somatic mutations in lung cancer, providing a general image of the lung cancer genome and a suitable approach of therapeutical objectives.

Conflict of interests

None to declare.

Funding

The research presented in this paper has been supported by Funding Contract no. 211 with OI – ANCS signed on 20.07.2010, within POS CE Operational Programme, Priority Axis 2 – CDI competitiveness – major Field of Intervention D.2.1. “Research-development in partnerships between research-development universities/institutes and enterprises for result attainment applicable in economy”, Operation 2.1.2.: “High level scientific CD projects with specialists from abroad”, Project title GENE PROFILE OF NON-SMALL CELLS PRIMITIVE BRONCHOPULMONARY CANCERS AND INVASION OF MEDIASTINAL GANGLIA, Project number/Code SMIS 692/12650, unfolded between 20.07.2010 - 30.06.2014.


57. Hammerman PS, Sos ML, Ramos AH, et al. Mutations in the 


53. Berghoorn K, Shaw AT, Ou SH, et al. ROS1 rearrangements 


51. Charest A, Lane K, McMahon K, et al. Fusion of FIG to the 


48. Graus-Porta D, Beerli RR, Daly JM, Hynes NE. ERBB-2, the pre-

47. Jørgensen JT. Targeted HER2 treatment in advanced gastric 

46. Peruzzi B, Bottaro DP. Targeting the c-Met signaling pathway in 

45. Yoshida A, Kohno T, Tsuha K, et al. ROS1-rearranged lung 

44. Turner N, Grose R. Fibroblast growth factor signalling: from 

43. Hammerman PS, SOS ML, Rames AH, et al. Mutations in the 

42. Eder JP, Shapiro GI, Appleman LJ, et al. A phase I study of fore-

41. Schubbert S, Shannon K, Bollag G. Hyperactive Ras in 

40. Spigel DR, Burris HA 3rd, Greco FA, et al. Randomized, 

39. Ogasawara Y, Yano M, Fujii Y. PIK3CA mutation status in 

38. gene amplification or by splice mutations deleting the 


36. NM23-H1, Shigeta S, Williams J, et al. Clinical significance of 

35. Atanassova U, Novoselsky A, Ovchinnikov S. Amplification of 


