Review Article

Implications of Insulin-like Growth Factor 1 Receptor Activation in Lung Cancer

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Abstract

Insulin-like growth factor 1 receptor (IGF1R) has been intensively investigated in many preclinical studies using cell lines and animal models, and the results have provided important knowledge to help improve the understanding of cancer biology. IGF1R is highly expressed in patients with lung cancer, and high levels of circulating insulin-like growth factor 1 (IGF1), the main ligand for IGF1R, increases the risk of developing lung malignancy in the future. Several phase I clinical trials have supported the potential use of an IGF1R-targeted strategy for cancer, including lung cancer. However, the negative results from phase III studies need further attention, especially in selecting patients with specific molecular signatures, who will gain benefits from IGF1R inhibitors with minimal side effects. This review will discuss the basic concept of IGF1R in lung cancer biology, such as epithelial-mesenchymal transition (EMT) induction and cancer stem cell (CSC) maintenance, and also the clinical implications of IGF1R for lung cancer patients, such as prognostic value and cancer therapy resistance.

Keywords: *IGF1R, epithelial-mesenchymal transition, cancer stem cells, chemotherapy, resistance, clinical trials*

Introduction

Cancer cells rely on a particular driver-oncogene that promotes cell proliferation and resistance to apoptosis (1). Among the driver-oncogenes, receptor tyrosine kinase (RTK) plays an important role in the carcinogenesis of various cancers. Because RTK is actionable, it is very promising for targeted treatment. One of the RTKs that has attracted attention in the last decade is insulin-like growth factor 1 receptor (IGF1R).

Insulin-Like Growth Factor 1 Receptor

IGF1R is a transmembrane heterotetrameric protein that promotes transformation toward malignancy and cancer cell proliferation and survival (2). As an RTK, IGF1R is expressed in various human cell types and tissues, and is quite similar to insulin receptor (IR). However, the receptors have different roles: IGF1R regulates cell apoptosis, growth, and differentiation, while IR controls physiological systems related to metabolism (3). IGF1R can be stimulated by its ligands: insulin-like growth factor 1 (IGF1) or insulin-like growth factor 2 (IGF2) (4). IGF1R could also be activated by insulin, especially at high concentrations (5, 6). Upon activation, IGF1R triggers downstream signals involving important pathways, such as RAS–RAF–MAPK and phosphoinositide 3-kinase (PI3K)–AKT, consequently regulating a variety of cellular processes in both the physiologic and the diseased state (7).

IGF1 is produced in the liver under the stimulus of growth hormone (GH) acting on the GH receptor (GHR) (8). Under physiologic conditions, IGF1 is the main mediator of GH's effects; therefore, it has a strong impact on cell proliferation and differentiation and is a strong apoptosis inhibitor (9). A high plasma level of IGF1 is related to an increased risk of lung malignancy (10, 11), and patients with lung cancer have shown significantly increased circulating IGF1 levels compared to a healthy control group ($P < 0.05$) (12). A meta-analysis affirmed that

genetic variation of the IGF1-IGF1R axis may be the main determinant for lung cancer risk (13). IGF1 plays a key role in carcinogenesis among patients with type 2 diabetes mellitus (14, 15). An animal study showed that the consumption of green tea polyphenols reduced cancer progression through reduction of IGF1 levels (16).

The dysregulation of IGF1R signalling has been implicated as a critical contributor to cancer cell proliferation, migration, and resistance to anticancer therapies (17). IGF1R overexpression enhances angiogenesis, indicated by a higher vessel density (18). Moreover, IGF1R activation contributes to the inhibition of apoptosis, anchorage-independent growth, and tumour-associated inflammation (19). Evidence also suggests that this pathway has been implicated in many aspects of metastasis (20). Downregulation of IGF1R has been shown to inhibit cancer cell proliferation (21).

Regulation of IGF1R expression

IGF1R gene transcription is regulated by multiple interactions that involve DNA-binding and non-DNA-binding transcription factors (22). DNA-binding transcription factors that have been shown to be involved in the regulation of IGF1R gene transcription are zinc-finger protein Sp1, E2F1, EWS-WT1, high-mobility group A1 (HMGA1), and Krüppel-like factor-6 (KLF6) (23). One of the major transcription factors responsible for regulating expression of the IGF1R gene is the product of the Wilms tumour suppressor gene WT1, in which the protein product is capable of binding to the promoter region in the IGF1R receptor sequences, suppressing transcription (24).

Expression of IGF1R in lung cancer

IGF1R has been well-studied for prognostic predictions in various malignancies, such as breast cancer (25), prostate cancer (26), head and neck carcinoma (27), colon cancer (28), brain cancer (29), and lung cancer (30, 31). Some lung cancers with implications for IGF1R include non-small cell lung cancer (NSCLC), adenocarcinoma (32), squamous cell carcinoma (SCC) (33), and small cell lung cancer (SCLC) (34). In one report, significant IGF1R expression was found in 53.8% of NSCLC patients, with the SCC subtype showing a higher expression than non-SCCs (62.6% vs. 37.3%, respectively; $P = 0.0004$) (35). This finding was consistent with other studies suggesting that IGF1R protein expression is frequent in SCC compared with other NSCLC subtypes (36, 37). In one study, activation of IGF1R in NSCLC specimens was related to a history of tobacco use, mutant KRAS, and wild-type (WT) EGFR (38).

In the following sections, we describe the role of IGF1R activation in lung cancer biology, such as epithelial mesenchymal transition (EMT) induction and cancer stem cell (CSC) maintenance. We also discuss the clinical implications of the IGF1R signalling pathway, including resistance to chemotherapy, targeted therapy, and radiotherapy, as well as the prognostic role of IGF1R expression in lung cancer patients. Finally, we explore the impact of IGF1R inhibition in lung cancer from various preclinical studies and phase I, II, and III clinical trials.

IGF1R and the Biology of Lung Cancer

Involvement of IGF1R in epithelial-to-mesenchymal transition in lung cancer

Epithelial-to-mesenchymal transitions (EMTs) are trans-differentiation processes characterised by the detachment of cell-to-cell junctions and attenuation of apico-basolateral polarity, resulting in a migratory mesenchymal cell formation with invasive features (39). A growing body of evidence suggests that IGF1R plays a key role in animal models of lung cancer metastasis (40–42). EMT phenomena, as the basic mechanism of metastasis, have been associated with IGF1R activation in NSCLC (30, 43). IGF1 can induce transcription of EMT inducers, including E-cadherin transcriptional regulators, such as ZEB1 and Snail (44). We have previously demonstrated that activation of IGF1R plays a role in the EMT process induced by hypoxic conditions, a common microenvironment in solid tumours, in NSCLC cells (45). In our study, hypoxia caused accumulated hypoxia-inducible factor 1α (HIF-1α), resulting in increased production of IGF1. In an autocrine fashion, IGF1 then activates IGF1R. Moreover, we demonstrated that direct stimulation of IGF1R by IGF1 induced EMT in normoxic conditions. Meanwhile IGF2, also a ligand of IGF1R, was shown to be capable of inducing EMT (46). Another study showed that IGF1R also mediated transforming growth factor-β1 (TGFβ1)-induced EMT in the PC9 lung adenocarcinoma cell line (47).

Role of IGF1R in cancer stem cell maintenance in lung cancer

Epithelial tissues use paracrine and autocrine ligand activation of IGF1R signalling to maintain self-renewal of the basal cells, while in epithelial-derived cancers, IGF1R pathway hyperactivation promotes tumour progression and expansion (48). CSCs are equipped with a self-renewal ability; they can make exact copies of themselves, generating the rapidly dividing progeny that comprise tumours (49). Lung CSCs rely on activated IGF1R from IGF2 that is secreted from cancer-associated fibroblasts (50). The activation of IGF1R then promotes and maintains stemness in lung cancer. Furthermore, evidence from our *in vitro* model showed that IGF1R activation participates in the generation of CSCs under hypoxic conditions (51). In one study, IGF1R-mediated stemness in lung cancer could be inhibited by fibulins, a family of extracellular matrix proteins with tumour-suppressing features (52). Immunohistochemical analysis of specimens from lung adenocarcinoma patients showed that high expression of IGF1R was correlated with the CSC markers' expression of aldehyde dehydrogenase 1 family member A1 (ALDH1A1) and CD133 (53).

IGF1R and Clinical Implications in Lung Cancer

Role of IGF1R in resistance to chemotherapy and targeted therapy in lung cancer

IGF1R signalling dysregulation has deep implications for the response of tumours to current standard-of-care therapy (54). Accumulated evidence suggests that activation of IGF1R plays an important role in the resistance of NSCLC to platinum-based therapies (55, 56) and radiotherapy (57-59). One of the key downstream features of IGF1R that is involved in IGF1R-mediated cancer therapy is the activation of the PI3K-Akt signal transduction pathway (60). Interestingly, resistance of cancer cells to PI3K-Akt inhibitor also involves activation of IGF1R (61).

The resistance of lung cancer to various RTKs is related to the activation of IGF1R, which explains the bypass mechanism of this resistance. Our previous study revealed that IGF1R activation was involved in the gefitinib resistance induced by hypoxic conditions in NSCLC (51). IGF1R signalling mediates the resistance of EGFR-mutant T790M-positive NSCLC cells to afatinib (62). Activation of IGF1R is also involved in the resistance of NSCLC, harbouring rearrangements of anaplastic lymphoma kinase (ALK) to ALK-tyrosine kinase inhibitor (TKI) crizotinib (63). Finally, IGF1R was activated in resistant NSCLC cells to the histone deacetylase (HDAC) inhibitor, vorinostat (64). A summary of IGF1R's involvement in various mechanisms of resistance to cancer therapy is provided in Table 1.

Role of IGF1R expression as a prognostic factor in lung cancer

The role of IGF1R as a prognostic factor in lung cancer has been controversial. In one study, there were no differences observed in terms of survival between the IGF1R-expressing group and the non-expressing group in stage I–IIIA, surgically resected NSCLC patients (65). However, Nakagawa et al. found that IGF1R expression resulted in reduced disease-free survival (DFS), correlating with postoperative recurrence in lung adenocarcinoma (66). One meta-analysis that was performed to confirm the prognostic value of IGF1R expression suggested that IGF1R expression was correlated to an unfavourable DFS in patients with NSCLC (67). Moreover, IGF1R expression-scoring using immunohistochemistry methods was associated with stage of disease in NSCLC (68).

Table 1: IGF1R mediates resistance of lung cancer to cancer therapy

Mechanism of resistant	Cancer therapy resistant	References
Bypass signaling through IGF1R activation	Cisplatin	53,54,100
	Etoposide	54,61
	Radiotherapy	54-57
	EGFR-TKIs	41,49,60,70,101,102
	Crizotinib	61,77

Abbreviations: IGF1R, insulin-like growth factor 1 receptor; EGFR-TKIs, epidermal growth factor receptor-tyrosine kinase inhibitors.

A growing body of evidence shows that IGF1R expression is a biomarker for intrinsic resistance to EGFR-TKI (69, 70). IGF1R expression has also been shown to be associated with a reduced progression-free survival (PFS) after EGFR-TKI treatment in EGFR-mutant NSCLC cases (71). These findings open the door to a new strategy for overcoming resistance to EGFR-TKI, as it has been reported that IGF1R inhibition overcomes gefitinib resistance in lung adenocarcinoma (72).

IGF1R Inhibition in Lung Cancer

Basic principles of the IGF1R inhibition strategy

The fact that the IGFR pathway is a druggable target opens a new avenue for the development of novel therapies and for gaining more comprehensive knowledge about the implications of the IGF1 axis in carcinogenesis and tumour progression (73). The therapeutic strategy for IGF1R consists of three major approaches: (i) inhibition of tyrosine kinase (both ATP antagonists as well as non-ATP antagonists); (ii) ligand neutralisation using monoclonal antibodies that target the ligand; and (iii) blockade of receptors by monoclonal antibodies (74). In addition, small-interfering RNA (siRNA) against IGF1R also showed a sufficient suppression level to reduce IGF1R expression *in vitro* (75). The above-mentioned agents have the same type of effects in IGF1R, but they are distinguishable in the spectrum of target inhibition, pharmacological aspects, and mechanism of action (4). Antibodies to IGF1R attenuate ligand-binding and promote receptor degradation, causing downregulation of IR in IGF1R-expressing cells (76). The common adverse effects of IGF1 inhibitor are hyperglycaemia, nausea, vomiting, fatigue, anorexia, and skin reactions (77).

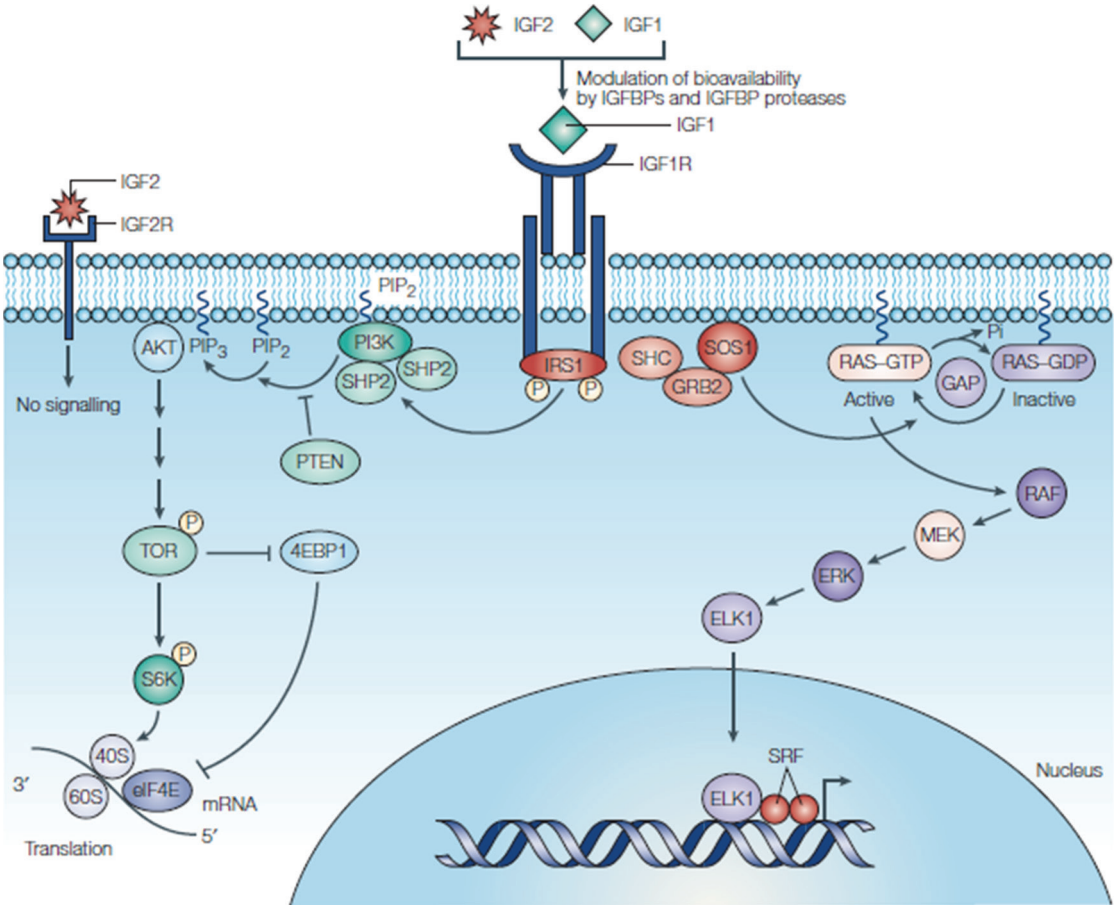

Figure 1: IGF1R signaling pathways. Abbreviations: [Reprinted by permission from Macmillan Publishers Ltd: Nature Review Cancer 4:505 – 518, copyright 2004].

IGFR TKI in lung cancer

After successful experience with using small-molecule receptor TKIs, such as gefitinib and erlotinib, IGF1R TKI has become one of the most thoroughly studied strategies for IGF1R inhibition (78). The advantages of small-molecule TKIs are their ability to cross the blood–brain barrier and to be given orally. It has been reported that if IGF1R alone is blocked, unexpected signalling through the IR can cause persistent NSCLC cell growth, which is the case for monoclonal antibodies (79). An advantage of small-molecule IGF1R TKIs over monoclonal antibodies is their capacity to inhibit IR as well, so that it is less susceptible to resistance to IGF1R-targeted therapy (80).

There are two categories of IGF1R TKI: ATP antagonists (OSI-906, INSM-18, NVP-AEW541, NVPADW742, BMS-554417, and BMS-536924), and non-ATP antagonists (AG-1024 and BVP-51004 [PPP]) (80). OSI-906 is a selective and orally bioavailable IGF1R-IR TKI that displays potent inhibition of IGF1R and IR phosphorylation, and 906 has been shown to attenuate downstream pathway activation, including pERK1/2, pAkt, and p-p70S6K (81). Another ATP antagonist type of IGFR TKI, NVP-AEW541, attenuates IGFI-induced colony formation and survival of cancer cells through the inhibition of IGF-IR autophosphorylation (82). In our model, NVP-AEW541 is capable of restoring sensitivity of NSCLC cells to EGFR-TKI after they previously exhibited acquired resistance under hypoxic conditions (51). Furthermore, NVP-ADW742 has been shown to enhance the sensitivity of SCLC cells to carboplatin and etoposide (83). In an *in vitro* study, AG1024 showed anti-proliferative effects in two NSCLC cell lines, A549 and H1299 (84). Interestingly, AG1024 also had an inhibition effect on c-kit, which provides additional potential benefits for treating SCLCs, which are usually driven by both the c-kit protein tyrosine receptor kinase and IGF1R (85). Lastly, BVP-51004 is a non-ATP antagonist of TKI that can downregulate IGFIR through the induction of ubiquitination-mediated degradation (86).

Clinical studies of IGF1R-targeted therapy

The IGF1R-targeted agents that have been used in pre-clinical and/or clinical studies are: the small-molecule inhibitors linsitinib (OSI-906),

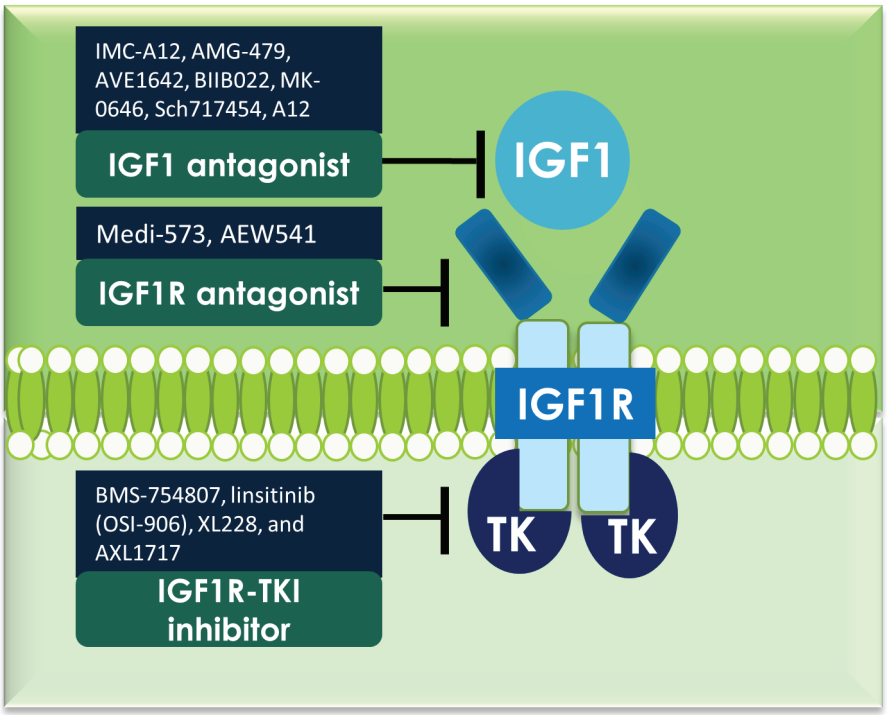

Figure 2: Strategies to inhibit IGF1R: Monoclonal antibody anti-IGF1R; neutralising antibody anti-IGF1, and; small molecule IGF1R-TKI

BMS-754807, AXL1717, and XL228; the ligand-neutralising antibody Medi-573; and monoclonal antibodies, such as AMG-479, cixutumumab (IMC-A12), BIIB022, AVE1642, robatumumab (Sch717454), and dalotuzumab (MK-0646) (87). One *in vitro* study showed that crizotinib also has an inhibitory effect on IGF1R (88).

As discussed above, IGF1R signalling has been shown to play a role in resistance to gefitinib and erlotinib in NSCLCs harbouring EGFR mutations, and in the generation of crizotinib-resistant cells in NSCLCs with ALK rearrangement. Therefore, one of the potential benefits of the IGF1R inhibition strategy is to overcome resistance to various TKIs. Another study showed that inhibition of IGF1R sensitizes cancer cells to carboplatin (89), paclitaxel (90), docetaxel (91), and vinorelbine (92).

IGF1R inhibition could also serve as a means to sensitize cancer cells to radiotherapy. In an *in vitro* and *in vivo* study, Iwasa et al. (93) showed that the IGF1R monoclonal antibody figitumumab effectively sensitized NSCLC cells to radiotherapy. Combined treatment with IGF1R monoclonal antibody A12 and radiation also resulted in delayed growth in A549, an adenocarcinoma cell line, in a xenograft mouse model (94).

Several phase I studies that involved solid tumours and investigated the safety of monoclonal antibodies against IGF1R, such as R1507 (95), dalotuzumab (MK-0646) (96), AMG 479 (97), cixutumumab (98), and figitumumab (99), have shown that these drugs are well-tolerated and display antitumour activity. Due to poor efficacy and excessive premature deaths with cixutumumab, its development was discontinued (100). In phase I/II randomised clinical trials, dalotuzumab plus erlotinib has resulted in better PFS, but not overall survival (OS), compared to erlotinib alone for NSCLC (101). For lung cancer, there has not yet been a phase III trial testing the efficacy of dalotuzumab, although a phase III study on colon cancer was prematurely discontinued because dalotuzumab resulted in shorter PFS (102).

One of the most controversial IGF1R-targeted therapies in lung cancer has been figitumumab. Figitumumab is a highly potent human-derived immunoglobulin G2 monoclonal antibody that works specifically against IGF1R (103). A controversial phase II trial suggested that a combination of chemotherapy and figitumumab for NSCLC provided benefits in terms of PFS and the objective response rate (104). However, this report was retracted following a thorough investigation of the analysis of OS and PFS in the results (105). In another phase III clinical study, the addition of figitumumab to standard platinum-based chemotherapy did not offer better OS in advanced-stage NSCLC patients with non-adenocarcinoma histology (106). Another phase III trial that determined the efficacy of erlotinib compared with erlotinib plus figitumumab in pre-treated NSCLC patients was terminated because the safety limit was crossed; the median OS was 6.2 months for erlotinib alone and 5.7 months for erlotinib plus figitumumab (107). After these trials, the development of figitumumab for IGF1R-targeted approaches was discontinued. Another negative result was obtained in a phase II clinical trial that tested the efficacy of R1507, a human immunoglobulin G1 recombinant monoclonal antibody specific to IGF1R, in combination with erlotinib (108). The results of that trial showed that co-administration of erlotinib with R1507 failed to offer better PFS compared to erlotinib alone in unselected advanced NSCLC subjects.

Explanations for these failures include the common signals of the IR and IGF1R systems, the common shared pathways for survival and growth, and suboptimal marker selection (4). Determining the specificity of a targeted agent against its specific target in a patient is not an easy task because it is difficult to obtain multiple biopsies for IGF1R expression analysis before, during, and after treatment (109). Moreover, although studies have demonstrated that sensitivity of NSCLC cells to IGF1R inhibition is dependent on IGF1R expression (110), detection of IGF1R expression is sometimes insufficient to predict the patient's response to IGF1R inhibition, as most tumours' growth does not rely on a single signalling pathway (109).

Despite these negative findings, it has still been necessary to consider circulating IGF1 in lung cancer patients who may benefit from IGF1R-targeted therapy (111). This concept is consistent with the previous evidence that high levels of circulating IGF1 will increase the risk of developing lung cancer in the future. Other predictive biomarkers that are under investigation are IRS2, IGFBP5, and MYB in colorectal cancer; IGF2, IRS-1, and IRS-2 in breast cancer; and IGF-1, IGF-2, and IGFBP-3 in pancreatic cancer (76).

Conclusions

The IGF1R signalling pathway has been implicated in lung cancer biology, contributing to the pathogenesis and behaviour of this

malignancy. In the last decade, advanced research has identified IGF1R as an actionable target. Although accumulated pre-clinical studies have revealed the implications of IGF1R in lung cancer biology, such as the EMT process, CSC maintenance, and resistant to cancer therapies, the negative findings of clinical trials using unselected lung cancer patients have been disappointing. However, these results should not discourage clinical investigators from developing future strategies for clinical trials involving more specific patients.

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Conception and design : FN, SLA
Analysis and interpretation of the data: SLA, ES, KT
Drafting of the article: FN
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Final approval of the article: SLE, FT, ES, KT
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