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PERSONALIZED MEDICINE FOR EFFECTIVE TREATMENT OF NON-SMALL-CELL LUNG CANCER WITH TARGETED THERAPIES

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ABSTRACT

Lung cancer is the most common cause of cancer death worldwide, with most deaths having distant metastases. It has become increasingly complex to get effective treatment for lung cancer patients. While generalized medicine with traditional therapy resulted in comparatively poor response, personalized medicine has been well known to be an important strategy for effective treatment of lung cancer, with current focus on significant detection of clinical oncogenic drivers responsible for tumor initiation and maintenance and development of drug resistance. In lung cancer, especially in non-small-cell lung cancer (NSCLC), EGFR, ALK, RET, ROS1, BRAF, KRAS, NRAS, PIK3CA, DDR2, MET, ERBB2 have been reported to be key oncogenic drivers, which are targeted in the development and application of targeted therapeutic drugs. Personalized medicine based on these oncogenic drivers is highly recommended for treatment of advanced NSCLC patients. In this article, the significant application of personalized medicine based on the key oncogenic drivers for effective treatment of NSCLC with targeted therapeutic drugs is reviewed.

Keywords: Personalized medicine, targeted therapy, non-small-cell lung cancer, treatment.

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INTRODUCTION

Lung cancer is the most frequently diagnosed human malignant tumor and remains the highest cancer-related cause of mortality in both sexes with approximately 2.1 million newly diagnosed cancer cases and 1.8 million cancer related-deaths each year worldwide (Bray et al., 2018). In 2018, there were 23667 newly diagnosed cases and 20710 deaths from this cancer in Vietnam. Despite significant advances made in both diagnostic and treatment approaches in recent years, the average 5 years survival rate remains at only 16% because the diagnosis is only conducted at advanced stages and consequently, patients have a very poor prognosis (Bray et al., 2015; Gridelli et al., 2015). Based on histopathological features, non-small-cell lung cancer (NSCLC) and small cell lung cancer (SCLC) accounts for 85% and 15% of all patients with lung cancer, respectively (Travis et al., 2013). NSCLC is divided into subtypes, being adenocarcinoma (ADC) and squamous cell carcinoma (SCC) (Travis et al., 2013). Furthermore, ADC represents 50% of cases among all lung cancer subtypes (Travis et al., 2013).

Personalized medicine, as defined by the National Cancer Institute (NCI), is a form of medicine using personal information about genes, proteins and environments for prevention, diagnosis and treatment of disease. Therefore, personalized medicine for NSCLC takes into consideration specific characteristics of each patient's tumor to prescribe the most effective approach for treatment. Especially, there has been a major change in the empirical treatment of NSCLC from using one drug for all to a targeted therapy by using the most effective drug for each patient (Li et al., 2013; Reungwetwattana & Dy, 2013). Furthermore, most advances in treatment using targeted therapy in NSCLC occurred in ADC due to the identification of targetable mutations being more common than in SCC. In NSCLC, personalized medicine based on targetable profiles of tumor such as EGFR (*EGFR* mutation, 20−30%), ALK (ALK rearrangement, 1–10%), RET (RET rearrangement, 1−2%), ROS1 (ROS1 rearrangement, 1−2%), BRAF (*BRAF* mutation, 2−5%), KRAS (*KRAS* mutations, 32%), NRAS (*NRAS* mutation, 2−3%), PIK3CA (*PI3KCA* mutation, 5−6%), DDR2 (*DDR2* mutation, 4%), MET (*MET* exon 14 skipping, 1−3%) and ERBB2 (ERBB2 amplication, 1−3% and *ERBB2* mutation, 2−4%) have been identified for effective treatment of NSCLC patients (Sharma et al., 2007; Suh et al., 2016; Rosas et al., 2019; Du et al., 2018; Bergethon et al., 2012; Lin, Shaw, 2017; Takeuchi et al., 2012; Farago, Azzoli, 2017; Guo et al., 2019; O'Leary et al., 2019; Aviel-Ronen et al., 2006; Vuong et al., 2018; Li et al., 2016).

Personalized medicine has been considered and integrated as a routine best practice for NSCLC patients with advanced stage from the year 2000 (Pfister et al., 2004). Then, to better understand the significant role of personalized medicine in NSCLC, this review summarizes the current personalized medicine strategies for effective treatment of NSCLC patients.

PERSONALIZED MEDICINE BASED ON TARGETABLE PROFILE OF TUMOR

EGFR mutation

EGFR, a transmembrane receptor protein with tyrosine kinase activity, has been well known to be involved in the pathogenesis of various types of cancer including NSCLC. Therefore, EGFR is the most attractive target for development of targeted therapy to treat cancer. The *EGFR* mutation, found in 20−30% of NSCLC with adenocarcinoma, showed potential for targeted therapies in clinical trials for the treatment of NSCLC (Sharma et al., 2007; Suh et al., 2016). The *EGFR* mutation is more prevalent in non-smokers and in the Asian population (Sharma et al., 2007; Shi et al., 2014).

Exon 19 deletion, exon 19 insertion, exon 20 insertion and missense mutation are four main types of *EGFR* mutations (Sharma et al., 2007). Of these, two most common mutation contents of *EGFR,* being exon 19 deletion (delE746-A750) and exon 21 missense mutation (L858R), are found in 90% of *EGFR*

mutations in NSCLC patients with adenocarcinoma. The second most common mutations of *EGFR* are frame deletion in exon 19 or point mutations in exon 18 and exon 21. The third most common mutation of *EGFR* is exon 20 insertion (Sharma et al., 2007).

Targeted therapeutic drugs have been used for effective treatment of NSCLC patients with indicated *EGFR* mutation (Table 1). However, all NSCLC patients harboring *EGFR* mutation will eventually become resistant to Erlotinib and Gefitinib (first-generation EGFR inhibitors). Acquired resistance due to the T790M mutation in exon 20 of *EGFR* is detected in 50−60% of cases with secondary resistance to first-generation EGFR inhibitors (Chong & Jänne, 2013). Afatinib and Dacomitinib (second-generation EGFR inhibitors) have been developed for such cases (Li et al., 2008). However, NSCLC patients with T790M would also develop resistance to Afatinib. Osimertinib, a third-generation EGFR inhibitor developed to treat NSCLC patients previously treated with Afatinib, is now approved by FDA, and recommended for treatment of *EGFR* T790M positive NSCLC patients (Mok et al., 2017).

ALK rearrangement and/or mutation

ALK, a transmembrane tyrosine kinase receptor, was identified specifically in NSCLC (Rikova et al., 2007). Rearrangement, point mutation and amplification are three types of oncogenesis in *ALK*.

ALK rearrangement, identified in approximately 1−10% of NSCLC patients, could benefit from targeted therapies for the treatment of NSCLC (Rosas et al., 2019; Du et al., 2018). To date, in NSCLC, 20 distinct ALK rearrangements have been detected, among which 11 are oncogenetic drivers, being EML4-ALK, KIF5B-ALK, KLC1-ALK, HIP1-ALK, BIRC6-ALK, PRKAR1A-ALK, PPM1B-ALK, EIF2AK3-ALK, BCL11A-ALK, CEBPZ-ALK and PICAM-ALK (Rosas et al., 2019; Du et al., 2018). Among these oncogenetic drivers, EML4-ALK, found in approximately 3−13% of all ALK arrangements, occurs most frequently in NSCLC (Inamura et al., 2008; Shaw et al., 2009; Sun et al., 2010; Horn & Pao, 2009; Du et al., 2018). ALK rearrangements are especially more common in younger adenocarcinoma patients who are non-smokers or light smokers (Camidge et al., 2010; Shaw et al., 2009). Targeted therapeutic drugs such as Crizotinib (first-generation inhibitor of ALK and MET), Ceritinib (second-generation inhibitor of ALK), Alectinib (inhibitor of ALK), Brigatinib (third-generation inhibitor of ALK and EGFR), and Lorlatinib (third-generation inhibitor of ALK and ROS1) have been used for the effective treatment of NSCLC patients with indicated ALK rearrangement and/or mutation (Table 1).

Another main type of oncogenesis in *ALK* is point mutation. Acquired resistance due to secondary mutations of *ALK* in NSCLC patients with ALK rearrangement treated with Crizotinib, are caused by mutations in the target *ALK* gene (Toyokawa & Seto, 2015; Lin et al., 2017). The secondary mutations of ALK, causing acquired resistance to ALK inhibitor such as Crizotinib, are 1151Tins, L1152R, C1156Y, F1174L, L1196M, L1198F, G1202R, S1206Y, G1269A, I1171T, D1203N and V1180L (Lin et al., 2017; Du et al., 2018). To treat effectively for NSCLC patients with ALK rearrangement previously treated with Crizotinib, Alectinib and Ceritinib have been developed (Shaw et al., 2014; Shaw et al., 2016). Afterwards, NSCLC patients with ALK rearrangement also develop resistance to Alectinib and/or Ceritinib due to new mutations in *ALK* such as as G1202R, for which Lorlatinib has been developed (Katayama, 2017).

ROS1 rearrangement

Rearrangement of ROS1, a receptor of the insulin receptor family with constitutive kinase activity, were found in NSCLC in 2007 (Rikova et al., 2007). ROS1 rearrangement, identified in 1−2% of NSCLC, could benefit from targeted therapies (Bergethon et al., 2012; Lin, Shaw, 2017). To date, 14 distinct ROS1 rearrangement have been detected in NSCLC, being CD74-ROS1, SDC4-ROS1,

SLC34A2-ROS1, EZR-ROS1, TPM3-ROS1, LRIG3-ROS1, FIG-ROS1, KDELR2-ROS1, CCDC6-ROS1, MSN-ROS1, TMEM106B-ROS1, TPD52L1-ROS1, CLTC-ROS1 and LIMA-ROS1 (Lin, Shaw, 2017). Among these contents of ROS1 rearrangements, CD74-ROS1 occurs most frequently in NSCLC (Gainor, Shaw, 2013). Crizotinib (inhibitor of ALK and MET) has been used for the effective treatment of NSCLC patients with indicated the ROS1 rearrangements (Table 1).

RET rearrangement

Rearrangement in *RET*, a proto-oncogene, were identified to be the result of transfection of the NIH3T3 cells with high molecular weight DNA of a human T-cell lymphoma (Takahashi et al., 1985). RET rearrangements found in 1−2% of NSCLC cases, could benefit from targeted therapies (Takeuchi et al., 2012; Farago, Azzoli, 2017). To date, the RET rearrangement detected in NSCLC are KIF5B-RET, CCDC6-RET, NCOA4-RET, EPH5-RET and PICALM-RET (Takeuchi et al., 2012; Farago, Azzoli, 2017). Among these, KIF5B-RET is the most common RET rearrangement in NSCLC (72%) (Takeuchi et al., 2012; Kohno et al., 2012; Farago, Azzoli, 2017). Targeted therapeutic drugs such as Cabozantinib (a multikinase inhibitor active against VEGFR2, MET, ROS1, AXL, KIT, TIE2 and RET), and Vandetanib (a multikinase inhibitor active against VEGFRs, EGFR, and RET) have been used for the effective treatment of NSCLC patients with indicated RET rearrangement (Table 1).

***BRAF* mutation**

BRAF, an intracellular serine/threonine kinase, activates the MAPK signaling pathway to regulate cell growth and proliferation. *BRAF* mutations, found in 2−5% of NSCLC cases, could benefit from targeted therapies (Suh et al., 2016; Guo et al., 2019; O'Leary et al., 2019). For NSCLC, missense mutation of *BRAF*, classified into V600E (90%) and non-V600E (G469L and Y472C) subtypes, mainly in current and former smokers (Marchetti et al., 2011; Cardarella et al., 2013). Especially, all NSCLC patients with the non-V600E subtypes are heavy smokers (Cardarella et al., 2013). Dabrafenib and/or Vemurafenib (BRAF inhibitor) have been used for the effective treatment of these NSCLC patients with indicated *BRAF* mutations (Table 1).

***KRAS* mutation**

KRAS, a member of the RAS family, activates the RAF/MAPK and PI3K signaling pathway to control cell growth and proliferation. *KRAS* mutations, found in up to 32% of NSCLC cases, could benefit from targeted therapies (Aviel-Ronen et al., 2006; Suh et al., 2016; Guo et al., 2019). In NSCLC the most common mutations of *KRAS* at codon 12 are G12C (43%), G12V (18%) and G12D (11%). Especially, *KRAS* mutation is predominantly associated with NSCLC patients who have adenocarcinoma and are non-Asian smokers (Aviel-Ronen et al., 2006). Targeted therapeutic drug such as Trametinib (MEK1/2 inhibitor) has been used for the effective treatment of NSCLC patients with indicated *KRAS* mutations (Table 1).

Furthermore, in NSCLC, *KRAS* mutations are well known as non-druggable targets that predict resistance to EGFR inhibitors such as Erlotinib and Gefitinib (Chong, Jänne, 2013) and to ALK inhibitors such as Crizotinib (Gainor et al., 2013), i.e. *KRAS* mutations are mutually exclusive with *EGFR* mutations and ALK rearrangements in NSCLC (Chong, Jänne, 2013; Gainor et al., 2013).

***NRAS* mutation**

NRAS, a member of RAS family and a GTPase related to KRAS, regulates cell growth, proliferation and differentiation. *NRAS* mutations, identified in approximately 2−3% of NSCLC case, could benefit from targeted therapies (Suh et al., 2016). *NRAS* mutations are more common in NSCLC patients being current/former smokers (Ohashi et al., 2013). Trametinib (MEK1/2 inhibitor) has been used for effective treatment of NSCLC patients with indicated N*RAS* mutations (Table 1).

***PI3KCA* mutation**

PI3KCA, a catalytic subunit of the class IA PI3K which is the member of a family of

heterodimeric kinases, plays an important role in the regulation of cell growth, survival and motility. PI3KCA amplification and mutation are two main types of aberrant activation of PI3K. Among them, *PI3KCA* mutations, found in approximately 5−6% of NSCLC patients, could benefit from targeted therapies (Suh et al., 2016; Guo et al., 2019). targeted therapeutic drugs such as Erlotinib and/or Gefitinib (EGFR inhibitor) have been used for the effective treatment of NSCLC patients with indicated *PI3KCA* mutation (Table 1).

DDR2 mutation

DDR2, a receptor tyrosine kinase binding collagen I and III as its endogenous ligand, promotes cell proliferation, migration and metastasis by regulation of EMT (Vogel et al., 1997; Labrador et al., 2001; Walsh et al., 2011). *DDR2* mutations, found in approximately 4% of NSCLC cases, could benefit from targeted therapies (Suh et al., 2016; Guo et al., 2019). Only one targeted therapeutic drug, Dasatinib (SRC inhibitor), has been used for the effective treatment of NSCLC patients with indicated *DDR2* mutation (Table 1).

MET mutation

MET, a transmembrane receptor tyrosine kinase, plays an important function in embryogenesis, tumor growth and metastasis. Amplification, activating point mutation and *MET* exon 14 skipping are three main types of *MET* gene alteration. Among them, *MET* exon 14 skipping, reported in approximately 1−3% of NSCLC patients, could benefit from targeted therapies (Suh et al., 2016; Vuong et al., 2018). Targeted therapeutic drugs such as Crizotinib (inhibitor of MET and ALK), Capmatinib (MET inhibitor) and/or Glesatinib (inhibitor of MET and AXL) have been used for the effective treatment of NSCLC patients with indicated mutations in *MET* exon 14 skipping (Table 1).

ERBB2 mutation

ERBB2, a member of the ERBB family, activates downstream signaling pathway to drive oncogenesis in several types of cancer including lung cancer when forming with other members of the ERBB family as EGFR (Yarden, Sliwkowski, 2001). ERBB2 amplication and mutations are found in 1−3% and 2−4% of NSCLC patients, respectively (Suh et al., 2016; Li et al., 2016). In ERBB2 aberration, exon 20 insertions could benefit from targeted therapies. Targeted therapeutic drugs such as Afatinib (EGFR inhibitor) and/or Neratinib (ERBB2 inhibitor) have been used for the effective treatment of NSCLC patients with indicated *ERBB2* mutation (Table 1).

Table 1. Personalized medicine with targeted therapeutic drugs for effective treatment of NSCLC patients harboring targetable profile

Oncogenic drivers	Types of Mutation/Rearrangement	Mutations/Fusions	Targeted therapy drugs
EGFR	Missense mutation	G719A	Erlotinib Gefitinib Afatinib Dacomitinib Osimertinib
		G719S	
		G719C	
		G719D	
		S768I	
		T790M	
		C797S	
		L858R	
		L861Q	
		L861R	
	Exon 19 deletion mutation	K745_A750delinsK	
		K745_T751delinsKI	

		K745_E746delinsK	
		K745_E749delinsK	
		K745_A750delinsKIP	
		K745_T751delinsKIP	
		K745_T751delinsKA	
		K745_T751delinsK	
		K745_T752delinsKI	
		K745_T752delinsKV	
		E746_A750del	
		E746_A751del	
		E746_T751delinsA	
		E746_T752delinsA	
		E746_T752delinsV	
		E746_T752delinsD	
		E746_A750delinsEP	
		E746_T751delinsEQ	
		E746_A750delinsRP	
		E746_A750delinsQP	
		E746_T751delinsS	
		E746_T751delinsI	
		E746_T751delinsIP	
		E746_T751delinsQ	
		E746_T751delinsL	
		E746_S752delinsI	
		E746_S752del	
		E746_P753delinsLS	
		E746_P753delinsIS	
		E746_A750delinsAP	
		E746_A750delinsVP	
		E746_A751delinsVA	
		E746_A751delinsVP	
		E746_A751delinsV	
		E746_P753delinsVS	
		E746_P753delinsVQ	
		E746_A750delinsDP	
		E746_T751delinsEP	
		E746_T751delinsE	
		E746_S752delinsEQH	
		E746_S752delinsEQ	
		E746_P753delinsE	
		L747_E749del	
		L747_A750delinsP	
		L747_T751delinsP	
		L747_T751del	
		L747_S752del	

		L747_P753delinsQ	
		L747_T751delinsS	
		L747_S752delinsS	
		L747_P753delinsS	
		L747_T751delinsQ	
		L747_T751delinsPT	
		L747_T751delinsA	
		L747_S752delinsQ	
		L747_S752delinsQH	
		L747_K754delinsANKG	
		L747_K754del	
		L747_A755delinsAN	
		L747_K754delinsST	
		L747_A755delinsSKG	
		E749_E758delinsE	
		E749_K754delinsE	
		A750_E758delinsP	
		A750_E758delinsA	
		A750_I759delinsAN	
		T751_I759delinsS	
		T751_I759delinsI	
		T751_I759delinsN	
		T751_I759delinsREA	
		T751_I759delinsT	
		S752_I759del	
		P753_I759del	
	Exon 19 insertion mutation	I744_K745insKIPVAI	
		K745_E746insIPVAIK	
		K745_E746insVPVAIK	
		K745_E746insTPVAIK	
	Exon 20 insertion mutation	M766_A767insASV	
		M766_A767insAI	
		A767_S768insTLA	
		S768_V769insVAS	
		V769_D770insGVV	
		V769_D770insGSV	
		V769_D770insDNV	
		V769_D770insCV	
		V769_D770insASV	
		D770_N771insY	
		D770_N771insSVD	
		D770_N771insNPH	
		D770_N771insN	
		D770_N771insGT	
		D770_N771insGL	

		D770_N771insGF	
		D770_N771insGD	
		D770_N771insG	
		D770_N771insAPW	
		N771delinsTH	
		N771delinsSH	
		N771delinsSGH	
		N771_P772insRH	
		N771_P772insN	
		N771_P772insH	
		P772_H773insV	
		P772_H773insTHP	
		P772_H773insHV	
		H773_V774insQ	
		H773_V774insPH	
		H773_V774insNPH	
		H773_V774insH	
		H773_V774insAH	
		V774_C775insHV	
ALK	Rearrangement	EML4-ALK	Crizotinib Ceritinib Alectinib Lorlatinib
		KIF5B-ALK	
		KLC1-ALK	
		HIP1-ALK	
		BIRC6-ALK	
		PRKAR1A-ALK	
		PPM1B-ALK	
		EIF2AK3-ALK	
		BCL11A-ALK	
		CEBPZ-ALK	
		PICAM-ALK	
	Missense mutation	1151Tins	
		L1152R	
		C1156Y	
		F1174L	
		L1196M	
		L1198F	
		G1202R	
		S1206Y	
		G1269A	
		I1171T	
		D1203N	
		V1180L	
ROS1	Rearrangement	CD74-ROS1	Crizotinib
		SDC4-ROS1	
		SLC34A2-ROS1	

		EZR-ROS1	
		TPM3-ROS1	
		LRIG3-ROS1	
		FIG-ROS1	
		KDELR2-ROS1	
		CCDC6-ROS1	
		MSN-ROS1	
		TMEM106B-ROS1	
		TPD52L1-ROS1	
		CLTC-ROS1	
		LIMA1-ROS1	
RET	Rearrangement	KIF5B-RET	Cabozatinib Vandetanib
		CCDC6-RET	
		NCOA4-RET	
		EPHA5-RET	
		PICALM-RET	
BRAF	Missense mutation	V600E	Vemurafenib Dabrafenib
		G469L	
		Y472C	
KRAS	Missense mutation	G12A	Trametinib
		G12D	
		G12V	
		G12S	
		G12R	
		G12C	
		G13D	
		G13C	
		G13R	
		G13S	
		G13A	
		Q61K	
		Q61L	
		Q61R	
		Q61H	
NRAS	Missense mutation	G12C	Trametinib
		G12R	
		G12S	
		G12A	
		G12D	
		Q61K	
		Q61L	
		Q61R	
		Q61H	
PIK3CA	Missense mutation	H1047R	Erlotinib

		H1047L	Gefitinib
DDR2	Missense mutation	S768R	Dasatinib
MET	Exon 14 skipping mutation	c.2888-18_2888-7del12	Crizotinib Capmatinib Glesatinib
		c.3024_3028+7del12	
		c.3001_3021del21	
		c.3028G>T	
		c.2888delA	
		c.3028G>A	
		c.3028G>C	
		c.3028+1G>T	
		c.2888-29_2888-6del24	
ERBB2	Exon 20 insertion mutation	G776delinsVC	Afatinib Neratinib
		V777_G778insCG	
		G778_S779insG	
		S779_P780insVGS	
		P780_Y781insGSP	
		G776Lfs*98	

CONCLUSION AND FUTURE PERSPECTIVES

Personalized medicine for effective treatment of NSCLC patients with *EGFR* mutations, ALK rearrangements and/or mutations, ROS1 rearrangements, RET rearrangements, *BRAF* mutations, *KRAS* mutations, *NRAS* mutations, *PIK3CA* mutations, *DDR2* mutations, *MET* mutations and *ERBB2* mutations has become the international standard of care for NSCLC patients (Fig. 1, Table 1). However, standardization and validation of detection methods for oncogenic drivers in NSCLC patients is very essential for accurate and reproducible results. Next-generation sequencing (NGS), a powerful detection method, will offer the vision of personalized medicine where an individual's treatment can be based on that patient's individual molecular profile, rather than on historical population-based medicine. NGS will be also the powerful method to identify new biomarkers for early diagnosis of lung cancer and is increasingly used to guide personalized treatments decisions for NSCLC patients.

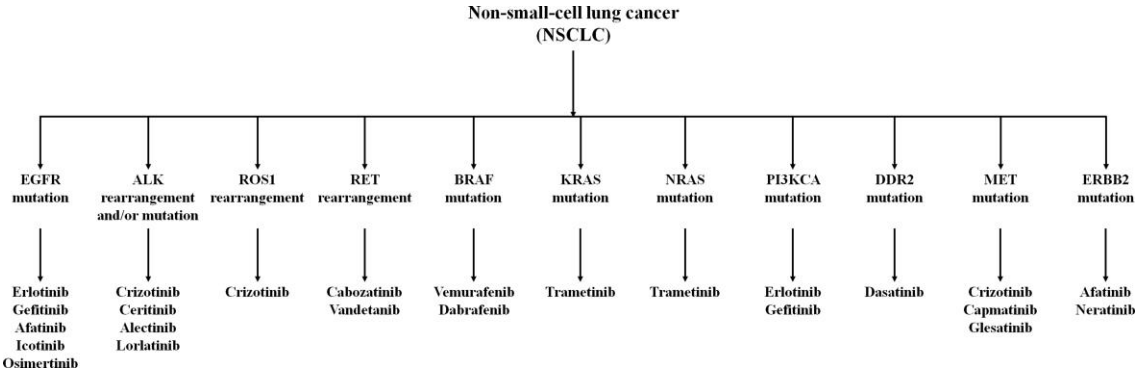

Figure 1. Personalized medicine with targeted therapeutic drugs for effective treatment of NSCLC patients harboring targetable profile

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