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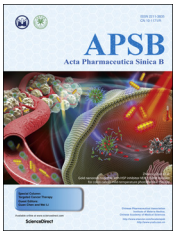

REVIEW

Personalized medicine in non-small cell lung cancer: a review from a pharmacogenomics perspective

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Abstract Non-small cell lung cancer is a prevalent and rapidly-expanding challenge to modern medicine. While generalized medicine with traditional chemotherapy yielded comparatively poor response rates and treatment results, the cornerstone of personalized medicine using genetic profiling to direct treatment has exalted the successes seen in the field and raised the standard for patient treatment in lung and other cancers. Here, we discuss the current state and advances in the field of personalized medicine for lung cancer, reviewing several of the mutation-targeting strategies that are approved for clinical use and how they are guided by patient genetic information. These classes include inhibitors of tyrosine kinase (TKI), anaplastic lymphoma kinase (ALK), and monoclonal antibodies. Selecting from these treatment plans and determining the optimal dosage requires in-depth genetic guidance with consideration towards not only the underlying target genes but also other factors such as individual metabolic capability and presence of resistance-conferring mutations both directly on the target gene and along its cascade(s). Finally, we provide our viewpoints on the future of personalized medicine in lung cancer, including target-based drug combination, mutation-guided drug design and the necessity for data of population genetics, to provide rough guidance on treating patients who are unable to get genetic testing.

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1. Introduction

Throughout the course of medical history, lung cancers have slowly but determinately expanded in prevalence and as a challenge to medical efforts on a global scale. Pollution from industrialization and lifestyles that are increasingly affected by unhealthy habits are the main known drivers behind this undeniable tend. Especially in China, lung cancer is the most prevalent type of cancer for not only males, but outstandingly, also for females, displacing even the usually predominant breast and cervical cancers[1]. This coupled with the lethality of lung cancer, which ranks on average as the deadliest type of cancer across the globe for both genders, issues a stark alarm for the need to not only address the notable causes of lung cancer, but also to invest in advancing the field for effective treatments[2]. Traditionally, our only options have been to classify patients by visible symptoms and treat them with various regiments (both pharmaceutically and other) until one elicits a positive response or until the patient succumbs. This strategy has left much to be desired as the death rate even with treatment remains so high that most patients do not survive their first year after diagnosis[3,4]. However, the upturn to this picture has been the advent of personalized medicine, spurred by the realization that despite similar phenotypes, lung cancers can be categorized and sorted by their underlying genetic causes and patients can be separated by their individual abilities to metabolize or otherwise make effective use of treatment compounds[5,6]. Over the recent years, increasingly successful implementation of the personalized approach to cancer treatment driven by the expansion of our knowledge on the genetic complications that affect lung cancer has greatly enhanced our understanding and ability to control the outcome for many patients diagnosed with the incurable condition[7,8]. Some examples of the more well-established and classical targets for personalized therapy include the K-Ras (KRAS), epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) pathways with the cytochrome P450 family taking the brunt of the metabolic pressure from chemotherapies. This review aims to touch upon the foundations, modern advances, possible future goals/directions and the limitations on currently US Food and Drug Administration (FDA)-approved personalized chemotherapy treatment regiments with specific genetic targets for patients with lung cancer from a pharmacogenomic perspective. Drugs that do not target specific cancer-inducing genes (such as the taxols, vinca alkyloids, DNA-replication inhibitors), drug candidates that have not yet earned FDA approval for use in NSCLC patients in the US and non-genetic factors influencing treatment are not discussed. Here, we argue for the benefit of revising our philosophy to cancer treatment in order to defeat resistance; instead of focusing completely on the major cancer-causing mutations and allowing other mutations to arise or minor mutations to take over from selective pressure, we should consider personalized cocktails that specifically target the driver cancer-causing mutation while simultaneously suppressing other sources of passenger carcinogenic mutations and pre-empting their arrival.

2. Tyrosine kinase inhibitors

Few anti-cancer strategies are as well-known as the tyrosine-kinase inhibitor (TKI) family. Overexpression of the EGFR family of proteins (EGFR/HER1, HER2, HER3, HER4) can activate cell survival/proliferation pathways such as phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) and proto-oncogenes (such as KRAS) leading to unchecked cell division and cause of certain types of cancers including lung cancers (Fig. 1). By acting as a competitive inhibitor to adenosine triphosphate (ATP) for its receptor site on EGFR, TKIs can prevent the EGFR homodimer from receiving the ATP molecule which it needs to phosphorylate the tyrosine amino acids into phosphotyrosine. Lack of this phosphorylated site prevents interaction with the proteins that require the phosphotyrosine site on activated EGFR to assemble their protein complexes and initiate their cascades. Thus, the TKI family of anti-cancer compounds aims to prevent EGFR overexpression from causing uncontrolled cellular proliferation by

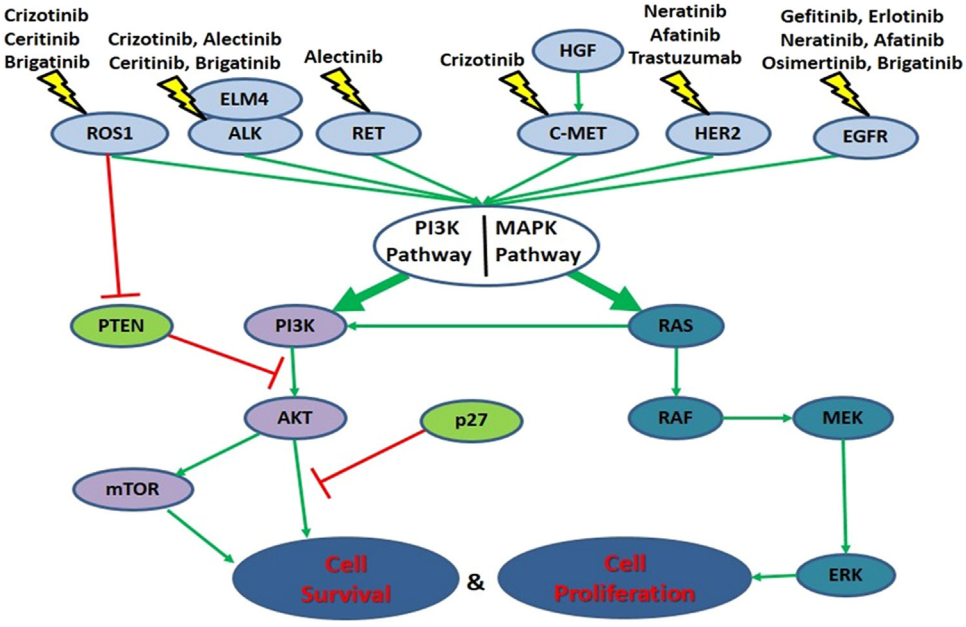

Figure 1 Major pathways of tumorigenesis and chemotherapy. Chemotherapies target the various activators of the PI3K and MAPK pathways which are the major buttresses of cancer progression.

hindering its activation. As of this review, there are three generations of TKIs, each aimed at defeating the mutations noted to render the last generation treatment ineffective. The first generation encompassed early drugs such as Gefitinib, Erlotinib, etc., the second contains chemotherapies such as Afatinib and Neratinib, and the most recent third generation treatments are flagshipped by Osimertinib (approved by the FDA In 2017).

Gauging the case-by-case appropriateness of treatment with TKIs is dependent on the genetic etiology of the lung cancer being determined as overexpression of EGFR or KRAS[9–12]. Of the current TKIs, Gefitinib is a first generation TKI and also the most well-documented answer to lung cancer patients confirmed with EGFR-based lung cancer. Guillermo Paez et al.[13] who worked with two lung cancer patient cohorts from Japan and the US first noted that, on average, Gefitinib was markedly more effective in the Japanese cohort than in the American counterpart. It was then noticed that of the two cohorts, 15 out of 58 patients in the Japanese cohort but only 1 out of 61 patients in the American cohort were harbored EGFR mutations. The group connected this finding to the observations that in other studies with American lung cancer patients responding well to Gefitinib, EGFR overexpression was especially prevalent. Specifically, while some mutations in EGFR such as L858R or delL747-S752 have been noted to confer enhanced advantages to ATP competitive inhibitors by creating a site with increased affinity to the compounds[14,15], other mutations such as T790M (gatekeeper), T854A, D761Y, L747S can introduce the opposite effect and cause Gefitinib resistance to arise[16,17]. Perhaps most thought-inciting, though, is that abnormal amplification in other genes of the same signaling cascade with EGFR can also cause resistance to Gefitinib in otherwise responsive tumors[18]. Engelman et al.[18] discovered that mesenchymal epithelial transition (MET) amplification was responsible for reducing the effectiveness of Gefitinib treatment in otherwise prime candidates with EGFR mutations by up-regulating HER3 thus activating the PI3K pathway independently of EGFR. MET can also activate the PI3K pathway by binding to hepatocyte growth factor (HGF) and thus, HGF hyperexpression acts as yet another pathway through which PI3K activation can bypass the EGFR cascade and evade inhibition by TKIs[17]. A similar situation where amplification (among other mechanisms including ATP-site alteration) was shown to lead to resistance is in the case of BCR-ABL derived chronic myeloid leukemia developing insensitivity to Imatinib[19]. As with each additional level of treatment option, patients stand a better chance. Shepherd et al.[20] documented that as an additional line of treatment for patients who have failed first or even second line chemotherapy, TKIs such as Erlotinib can provide another line of hope. In a cohort of 731 such patients, Shepherd's group found that Erlotinib treatment extended patient survival time by 42% or 2 months over the placebo[20,21]. However, the length of progression-free survival in patients seems to be affected by multiple factors (just as in other chemotherapies), such as the breast cancer gene 1 (BRCA1) expression level in lung cancer patients[22,23].

Modifying mutations that confer EGFR resistance are likely to explain why some studies have failed to elicit positive response in cancer patients positive for EGFR mutations though other factors such as epigenetics and environment may also play a part[24]. However, with these challenges also arise new opportunities as these additional factors can also become targets for cancer therapy in the second generation of TKIs. Neratinib is one such TKI that acts upon both EGFR (HER1) and the downstream HER2, though its results are modest and highly mutation-specific with resistance factors of its own[25–27]. In 2017, Gow et al.'s research showed the depth of mutation-specificity respective to the activity of three different TKIs against four commonly seen cancer-inducing HER2 mutations[28]. This demonstrated the need for the creation of a library of mutations with the various activity levels of different drugs to each mutation, a more detailed extension of the popular OncoKB online database. While the aforementioned TKIs all rely on cytochrome P450 liver enzymes for metabolism (CYP3A4 specifically), the irreversible inhibitor Afatinib is unique in that it is an active TKI without the need for metabolic processing, at least not by any liver enzyme[29]. This poses a unique opportunity both in that patients with abnormal CYP3A4 activity can safely use Afatinib but also, Afatinib may be used in combination with other liver-metabolized treatments without placing excessive burden on hepatic function[30]. Despite this unique quality, Afatinib is also affected by many resistance mutations including those that confer resistance to other TKIs[31,32]. Although there is evidence to suggest that Afatinib may be partially active against the T790M mutation, the effectiveness is controversial[33–36].

The bane of TKI treatment in terms of resistance development is without a doubt the T790M gatekeeper mutation, which is estimated to arise in at least half of all cases of resistant lung cancer[37]. The third and most recent generation of TKIs was developed to specifically combat this threat, with Osimertinib obtaining the first FDA approval in 2017. An irreversible inhibitor with over 600 times the killing capacity of Gefitinib (and over 40 times that of Afatinib) against T790M/L858R cancer cells *in vitro*, Osimertinib is recognized as the new go-to treatment for pretreated relapsed patients[37,38]. Indeed, Osimertinib showed an impressive ability to treat patients who had become insensitive to front line TKI treatments due to the T790M mutation in its clinical trials with as high as 71% response rate and 10.1 months progression-free survival in its phase 3 study[39]. Despite these successes, however, Osimertinib can exhibit significant side effects in patients as seen in all its later phase clinical studies[39–41]. In addition, it should not be regarded as a substitute or overall enhancement over other treatments in countering different resistance mutations as Osimertinib often exhibits lesser activity against an array of mutations (as well as the WT) compared other TKIs, especially Afatinib[37]. This could be due to fundamental differences in each drug's binding affinity to different or altered targets creating a unique resistance profile against an array of mutations for each compound. Finally, as Osimertinib is a much newer drug compared with other TKIs, resistant mutations to it have yet to be extensively characterized, however, studies already report several mutations around the gatekeeper site (such as the L792 position, G796D, C797S, etc.) to cause resistance to Osimertinib[42–44]. Non-EGFR gene-derived instances of resistance include Met amplification and the notorious V600E mutation in the BRAF proto-oncogene (which is downstream of EGFR)[45,46]. Together, they further iterate that Osimertinib and other upcoming third generation TKIs should mostly be regarded as specific tools for countering the T790M gatekeeper and not as replacements for previous generation TKIs.

3. Anaplastic lymphoma kinase inhibitors

Fusion of the ALK with echinoderm microtubule associated protein like 4 (EML-4) is another common origin of lung cancer[47]. Normally, they function towards proper neuronal development and microtubule formation, respectively, however when fused, they

can cause development of lung cancer by irregular activation of their downstream targets and represent 4%–7% of all non-small cell lung cancer cases[47] (Fig. 1). As such, the ALK inhibitor class drugs evolved to combat such cases of lung cancer[47]. Crizotinib is a class-leading ALK-inhibitor drug designed to target cases of lung cancer caused by activity of the EML4-ALK fusion protein by acting as a competitive inhibitor at the ATP binding pocket to shut down carcinogenic kinase activity[48]. In addition to this, Crizotinib is also a TKI inhibitor with anti-ROS1 and C-Met activities[48] (Fig. 1). Rearrangements in the ROS1 proto-oncogene and abnormal activation of C-Met promote tumor growth and evidence implicates both as causal agents in some cases of lung cancer[49,50]. Shaw's clinical trials of Crizotinib on 347 ALK-positive lung cancer patients showed an average of 4.7 months' increase in progression delay with over 3-fold increase in response rate as compared to other chemotherapies although no advantages in absolute remission were observed[51]. Clinical studies on the effects of Crizotinib on ROS1-rearranged lung cancer carried out by the same group on a 50-patient cohort showed a 72% response rate with a median response duration of 17.6 months and progression-free survival for 19.2 months, notably superior to the response seen in ALK-positive patients[49]. However, as with most drugs, challenges began to arise with the use of Crizotinib. In 2010, Choi et al.[52] reported a male lung cancer patient without any smoking history developing resistance to Crizotinib despite initial treatment success. This patient harbored two mutations in the ALK gene (C1156Y and L1196M) which the group transfected into mouse cells and performed a functional study showing reduced drug sensitivity and prevalent cell growth in the presence of different ALK inhibitors at various concentrations[52]. Doebele et al.[53] conducted a study on 14 ALK-positive patients who quickly fell back into tumor progression after initially promising treatment results and found two recurrent mutations on ALK (L1196M and G1269A) as well as two more copy number gains. Interestingly, the study also included mutations on EGFR (L858R) and KRAS (G12C and G12V) which implies that these genes may also affect the cellular reaction to Crizotinib perhaps indirectly as a component to a pathway or cascade[53]. Furthermore, that two independent patients both exhibited different KRAS mutations at amino acid position 12 implies that residue may play a critical role in mediating Crizotinib response. However, functional studies may suggest a modifying or secondary role since *in vitro* studies with KRAS G12V showed no resistance to Crizotinib when transfected alone into cells but when the same study was performed with direct patient-derived cell lines with G12C, resistance was clearly demonstrated[53]. In addition to finding several secondary variants with functional evidence of the resistance they confer to Crizotinib, Katayama et al.[54] showed the mechanisms by which mutations interfere with Crizotinib activity. The studies on ALK mutations showed marked drug resistance in L1196M, G1202R, S1206Y, 1151insT mutants by 3D modelling revealing that all four are near the Crizotinib-interacting ATP-binding pocket. L1196M was noted as a gatekeeper mutation, preventing the interaction between Crizotinib and the ATP-binding pocket[54]. G1202R and S1206Y are thought to reduce affinity to Crizotinib by changing the solvent-exposed region[54]. There are also notable mechanisms of resistance that are unrelated to the ATP-binding site. For example, C1156Y results in conformational changes to the entire binding cavity, thus reducing the ability of Crizotinib to reach the binding site, while L1152R represents an even more indirect form of disruption in that it diminishes Crizotinib's ability to affect downstream targets like AKT and ERK phosphorylation[17]. Although long-term strategies to overcome tumor resistance are always being researched, the most immediate and direct development has been new ALK-inhibitors such as Ceritinib which is sufficiently dissimilar from Crizotinib to circumvent most mechanisms of Crizotinib resistance[55]. In some cases, Ceritinib has demonstrated in clinical studies comparable or even superior anti-tumor activity than Crizotinib though significant issues with toxicity persist as can be seen in side effects including gastrointestinal discomfort, nausea, elevated aminotransferase, etc.[56]. Another example of a second-generation ALK inhibitor to succeed Crizotinib in the fight to circumvent resistance is Alectinib. In 2016, Skoulidis performed a critical study analyzing the effects of all Crizotinib, Ceritinib, and Alectinib on 14 different known resistance-conferring mutations on ALK, and noted that at least 12 of the 14 responded to one or more of the three treatments, further highlighting the importance of genetic determination before selecting treatment[57]. Despite this, one of the more amazing chemotherapies is Brigatinib, considered a second generation ALK-inhibitor approved by the FDA in 2017 for treatment against ALK, EGFR, and ROS1 mutation-induced cancers. Generally used as a final line of defense after patients no longer respond to Crizotinib, Brigatinib exhibits an impressive array of activity against resistance mutations including ALK L1196M, EGFR T790M, and even the Osimertinib-resistant EGFR C797S when paired with anti-EGFR monoclonal antibody treatments[58–60]. All-in-all, unlike generation III TKIs which focus on defeating the single most outstanding EGFR resistance mutation (T790M), Brigatinib and other second generation ALK inhibitors seem to be adept at busting many of the resistance mutations that can circumvent treatment by earlier ALK inhibitors.

4. Antibody-mediated treatment

Of the drugs discussed so far, the philosophy has been virtually the same: bind the ATP pocket as a competitive inhibitor to deny the offending gene its energy base for activation. However, monoclonal antibodies offer a different approach to lung cancer. Monoclonal antibodies approved by the US FDA for use in lung cancer patients typically target the interaction between the programmed death-ligand 1 (PD-L1) and the programmed cell death protein 1 (PD-1) receptor which helps facilitate the immune cascade through which the body recognizes and destroys cancer cells by T-cell-mediated response. PD-L1 is a protein responsible for autoimmune protection which may be overexpressed in cancer cells, preventing them from being destroyed by the body's natural immune defenses. By binding to and blocking the PD-1 receptor, anti-PD-L1 monoclonal antibodies stifle the cancer cells' defenses and provides the body's natural immune cascades a chance to attack the tumor cells (Fig. 2). However, this approach contains foundational weaknesses already seen in chemotherapy treatment. Because there are many receptor-ligand reactions that modulate T-cell recognition and inactivation against tumor cells (such as CD80/CD86 binding with cytotoxic T-lymphocyte-associated protein 4, CD155 with T cell immunoreceptor with Ig and ITIM domains, galectin-9 with hepatitis A virus cellular receptor 2, and other strategies such as indoleamine-pyrrole 2,3-dioxygenase increase to starve T-cells of tryptophan), blocking a single pathway usually fails to achieve any lasting effects (Fig. 2)[61,62].

Of the recent treatments approved including atezolizumab, nivolumab, and pembrolizumab, the mechanism of action is notably similar, with atezolizumab targeting the PD-L1 ligand

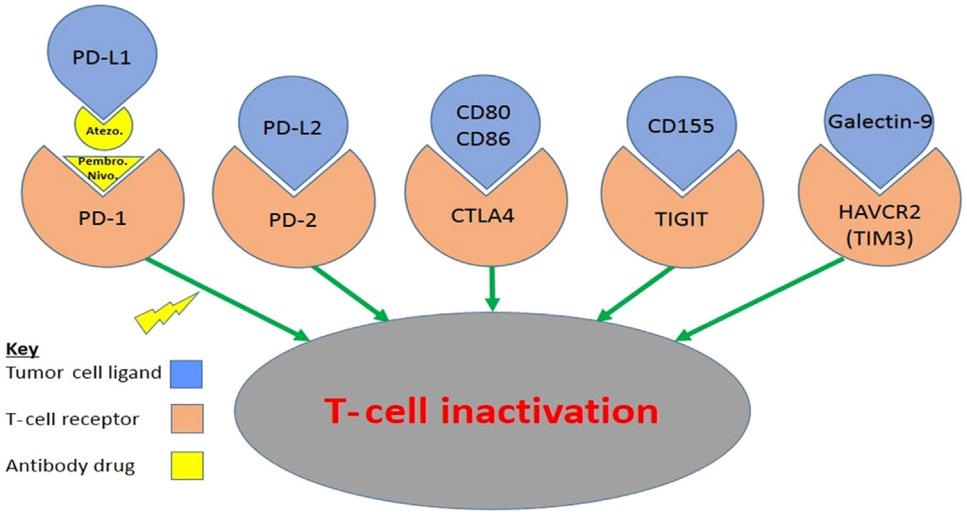

Figure 2 Pathways of T-cell inactivation and mechanisms of monoclonal antibodies. Pembrolizumab, Atezolizumab, and Nivolumab shut off the PD-1/PD-L1 T-cell inactivation pathway, one of many ligand-receptor pathways that contribute to T-Cell inactivation against tumor cells.

and the latter two targeting the PD-1 receptor[63–66]. Of these, pembrolizumab is the newest treatment, approved by the FDA in 2017 for use against cancers with hyper-expressed PD-L1. Many studies have shown the anti-cancer effects of pembrolizumab, including in comparison to currently available chemotherapies[67–69]. In 2016, Herbst conducted a study involving over 1000 PD-L1 elevated lung cancer patients in which he compared the effects of pembrolizumab in low concentration (2 mg/kg), high concentration (10 mg/kg), and docetaxel (a tubulin-targeting anti-cancer compound)[68]. The results showed a remarkable 49.4% increase in median survival time attained by high concentration treatment of pembrolizumab against treatment with docetaxel (12.7 months *vs*. 8.5 months; $P < 1.0 \times 10^{-4}$)[68]. The studies also put on display the predictive power of PD-L1 levels for pembrolizumab effect; when analyzing data from patients with greater than 50% tumor volume comprised of cells characterized by PD-L1 over-expression, the difference in survival time becomes much more dramatic[68]. For the same comparison between the high concentration pembrolizumab group *vs*. the docetaxel group, the difference in median survival time rose to a 111% increase in the Pembrolizumab group over the Docetaxel group (17.3 months *vs*. 8.2 months; $P < 1.0 \times 10^{-4}$)[68]. Reck et al.[69] obtained similar results in his studies showing a 66% increase in median progression-free survival time (10.3 months *vs*. 6.2 months; $P < 0.001$) when PD-L1 positive lung cancer patients were treated with pembrolizumab *versus* the various other chemotherapies assigned by the patients' primary care providers. Concurrently, Reck's study also found higher overall response rate (44.8% *vs*. 27.8%), response duration (>14.5 months *vs*. 6.3 months) and reduced severe adverse events occurrence (26.6% *vs*. 53.3%) in the pembrolizumab treated group[69]. Despite these successes, since pembrolizumab targets the body's avoidance mechanism against its own immune defenses, predictably, side-effects would involve autoimmune reactions and could be highly adverse for patients whom already exhibit genetic inclinations towards autoimmune disease. Furthermore, although extremely durable in response time compared to most chemotherapies, pembrolizumab is not impervious to resistance[70]. Pembrolizumab's effects may be modified not only by changes in the binding site between pembrolizumab and the PD-1 receptor (which have not been documented yet to the best of our knowledge), but also from mutations crippling the immunologic cascades that spearhead the body's response against recognized cancer cells[71]. Zaretsky's study on pembrolizumab-resistant patient samples showed that inactivating mutations in Janus kinase 1 (JAK1), Janus kinase 2 (JAK2), and $\beta 2$ microglobulin (B2M) conferred resistance by causing deficiencies to the immunological pathways for which pembrolizumab clears the way. As they are all components of cytokine cascades, (with B2M a direct component of major histocompatibility complex class I) the effects caused by loss of their functions could logically be assumed to also apply to the loss of function in other critical genes in these and other crucial cytokine cascades. Inversely, however, there is also data to show that patients with elevated expression of cluster of differentiation 8 (CD8) or higher numbers of $CD8^+$ T cells near the edge of the invasive tumor respond especially well to pembrolizumab treatment likely because these patients are naturally more immunologically-equipped to battle cancer tumors, though that ability is blocked by heightened PD-L1 repression[71]. Pembrolizumab is still a new drug and as such, there are still many points where resistance could arise that have yet to be documented. However, with the current level of knowledge, we can already see the benefit of personalized medicine to pembrolizumab. After determination of PD-L1 levels, expression of CD8, JAK1, JAK2, B2M, and a general evaluation of immunological health/capacity are all valuable for predicting whether Pembrolizumab is likely to be effective in individual patients.

5. Discussion

Personalized medicine has become indispensable to formulating effective treatment plans mainly due to the etiological diversity of lung cancer. However, resistance, both as a response to treatment and as an innate trait, is a complicating factor in personalized medicine as well as a lasting bane for effective cancer treatment[72]. Genetic determination for metabolic rate, proper target protein, and circumvention of natural resistance has become commonplace among the factors that physicians must consider when choosing the best line of therapy for their patients (Table 1). However, although it has become routine procedure to defer to genetic

Table 1 Pharmacogenomics of gene-targeted non-small cell lung cancer therapies.

Drug name	Drug class	Metabolic pathway (major)	Genetic target	Resistance
Gefitinib	Tyrosine kinase inhibitor: Gen. I	CYP3A4	EGFR	EGFR (T790M gatekeeper), KRAS, MET amplification, HGF over-expression
Erlotinib	Tyrosine kinase inhibitor: Gen. I	CYP3A4, CYP1A1	EGFR	EGFR (T790M gatekeeper), KRAS, MET amplification, HGF over-expression, BRCA1 expression
Neratinib	Tyrosine kinase inhibitor: Gen. II	CYP3A4	EGFR, HER2	EGFR (T790M gatekeeper), KRAS, MET amplification, HGF over-expression, HER2 (T798I gatekeeper)
Afatinib	Tyrosine kinase inhibitor: Gen. II	Minimal	EGFR, HER2	EGFR (Partial to T790M gatekeeper), KRAS, HGF over-expression, HER2 (T798I gatekeeper), SRC/ERBB3/c-KIT/c-MET, FGFR1
Osimertinib	Tyrosine kinase inhibitor: Gen. III	CYP3A4	EGFR	EGFR (mutations around gatekeeper but effective against T790M), BRAF V600E, MET amplification, more to be seen…
Crizotinib	Anaplastic lymphoma kinase inhibitor: Gen. I	CYP3A4, CYP3A5	ELM4-ALK, ROS1, c-Met	ALK (L1196M gatekeeper), EGFR, KRAS
Alectinib	Anaplastic lymphoma kinase inhibitor: Gen. II	CYP3A4	ALK, RET	ALK (effective against L1196M)
Ceritinib	Anaplastic lymphoma kinase inhibitor: Gen. II	CYP3A4	ALK, ROS1	ALK (effective against L1196M)
Brigatinib	Anaplastic lymphoma kinase inhibitor: Gen. II	CYP2C8, CYP3A4	ALK, EGFR, ROS1	ALK (effective against L1196M), EGFR (effective against T790M)
Atezolizumab	Monoclonal antibody	N/A	PD-L1	(Prospective) Immune deficiency, JAK1, JAK2, B2M, CD8 hypoexpression
Nivolumab	Monoclonal antibody	N/A	PD-L1	Immune deficiency, JAK1, JAK2, B2M, CD8 hypoexpression
Pembrolizumab	Monoclonal antibody	N/A	PD-L1	Immune deficiency, JAK1, JAK2, B2M, CD8 hypoexpression

Table 1. Presence of genetic target, resistance-conferring mutations and rate of drug metabolism must be considered when determining the proper treatment plan for each patient. Each drug of the different classes displayed a unique resistance profile, with some drugs vulnerable to and others unaffected by resistance-conferring mutations like gatekeepers. Specific mutations other than the gatekeepers are not shown though their genes are listed.

information for treatment strategies, our knowledge in this aspect still leaves much to be desired. The most obvious reminder of this is that even with all known genetic factors considered, the patient often still fails to respond to treatment leaving doctors at a loss for an answer. This speaks to other considerations in the microenvironment of the body requiring additional studies to understand as well as the diversity/heterogeneity of the tumor cells. Because of the latter, mono-target drugs that aim to kill cancer cells can experience initial success prolonging patient survival for several months but they eventually cause resistance to arise by adaptive tumor growth *via* alternative pathways to tumorigenesis. Fig. 1 shows several of the chemotherapy targets as activators of the PI3K and MAPK cell survival and proliferation pathways demonstrating the extensive routes that can be exploited by tumor adaptation to bypass shut-down of any single source and ultimately return to growth[73]. Rather, drugs that don't aim to simply kill off the population of tumor cells with their recognized target would largely circumvent this challenge. For example, differentiation inducers such as arsenic trioxide (As_2O_3, ATO) and all-trans retinoic acid (ATRA) represent a divergent approach to cancer therapy. While they specifically target the genes involved in acute promyelocytic leukemia (APL), PML (by ATO) and RARA (by ATRA), they aimed to induce differentiation instead of killing, which largely deprived the cancer cells of the adaptive incentive to diversify and develop resistance[74–77]. When used in combination therapy, ATO and ATRA have made the breakthrough of curing ALP, though they are not without significant side effects to multiple major organ systems[78,79]. With these drugs as positive examples, the future of cancer resistance circumvention for targeted therapies may further explore the path of differentiation induction, which is surely more complicated than those for cell growth. Thus, a possible response route to the heterogeneity of tumor composition lays in combination therapy. Cocktail treatment plans combining several drugs acting against different targets into a single treatment are known to be highly successful in treating tuberculosis, HIV and HCV patients[80,81]. Combination of ATO with ATRA is another example in the field of ALP treatment. A similar strategy of combining anti-cancer compounds by proportion of their targets in the tumor composition is an interesting idea that may lead to the development of "personalized cocktails" to mainly target all of the mutations within the tumor simultaneously while using trace amounts of other compatible chemotherapies to inhibit the rise of previously absent mutations. Due to the many complexities including target mutation, CYP450 subtypes, toxicity issues, possible drug-to-drug interference, and other factors from the body's (and tumor's) microenvironment, the creation of personalized cocktails for lung cancer therapy is still quite distant and requires more studies. However, these studies could potentially yield milestones in anti-cancer chemotherapy as well as resistance circumvention and become the new standard of treatment.

With enhanced understanding of lung cancer genetics (more pathways/components to pathways, population data, etc.), we may expand those horizons beyond pharmacogenomics onto other fields such as surgical outcome, likelihood of metastasis, etc. In areas where personalized genetic testing is not readily available, large scale population studies may serve as guides with information on the most prevalent metabolic phenotypes, genetic etiology/target of the lung cancer, and even the most common resistance mutations for certain populations and ethnicities. This would allow doctors to make better educated guesses on treatment plan when individualized genetic testing is not available/feasible[13,82]. Luckily, due to our realization of the importance of personalized medicine, endeavors to improve the precision and scope of personalized lung cancer treatment are plentiful[83–86]. As some patients may have mutations that confer a high degree of natural resistance to the drugs that their specific types of lung cancers require, perhaps a good future step is to develop derivatives of these drugs with tailored binding sites optimized to target the altered ATP-binding pockets. Although 3rd generation TKIs were made to defeat the most common gatekeeper T790M, other mutations still present significant challenges. Such an undertaking would be especially beneficial to the needs of patients with well-documented non-gatekeeper mutations hindering an otherwise clear treatment path. A good example would be development of a modified derivative of an established TKI with optimized affinity to the T854A ATP-binding pocket for patients with EFGR-hyperactive lung cancer with the T854A mutation.

In conclusion, although there is already a slew of information to guide healthcare providers in the implementation of personalized medicine for lung cancer patients, the need for further knowledge and ongoing genetics studies is clear. The possibilities discussed here and many more waiting to be explored would vastly enhance the state of personalized medicine for lung cancer patients as we know it today. And with the increasing incidence rate of lung cancer, especially in Asia, there has never been more dire need for such studies to push forward. Luckily, with the rising level of awareness and the current resources devoted, a bright future for personalized medicine and for lung cancer patients seems within our grasp.

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