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RESEARCH ARTICLE

Fifteen years of precision medicine in the lung cancer management: Perspectives and Challenges

Carlos Gil Ferreira#*, Pedro De Marchi*, Gilson Gabriel Viana Veloso, Marina Xavier Reis, Isabella Favato Barcelos, Tatiane Montella

Oncoclinicas&Co/MedSir, Brazil

***CGF and PDM contributed equally to this manuscript.**

#Corresponding author: carlosgil.ferreira@oncoclinicas.com

ABSTRACT

Precision medicine has revolutionized lung cancer management – particularly non-squamous cell carcinomas – with a broader genomic comprehension and the possibility of offering tailored treatments guided by oncogenic driver mutations – the basis of precision medicine. Since the publication of the IPASS trial in 2009 a new Era of molecular actionability began for lung cancer research and treatment. The remarkable past fifteen years were characterized by advances on genomic testing methodologies, the emergence of new biomarkers and targeted therapies, and the widespread of precision medicine in lung cancer care from advanced to earlier stages – specially for the adenocarcinoma histology, a heterogeneous disease with unprecedent improvements in outcomes. Nonetheless, several barriers need to be overcome with the adoption of cutting-edge technologies, such as the high cost of new diagnostic and therapeutical technologies and their discrepant accessibility, mainly in low- and middle-income countries. Moreover, there is still a lack of clear clinical actionability for squamous cell carcinoma and small cell lung cancer in which ideal biomarkers are yet to be discovered and validated. Herein, we aimed to discuss several aspects on how precision medicine positively impacted on lung cancer management and the lessons learned. Additionally, we scoped future perspectives on precision oncology in lung cancer as technology advances.

Keywords: lung cancer, precision medicine, thoracic oncology, next sequencing generation, health-care policies

Introduction

The burden of cancer care and cancer-related deaths continues to be a major challenge for global health[1]. Due to the need for new treatments, over 50% of ongoing clinical trials are related to cancer treatment, and, as a result, some landmark advances have been made[2].

Despite not being the most incident, lung cancer remains the deadliest cancer worldwide, accounting for 18% of all cancer deaths in 2020[3]. Several factors contribute to this high mortality, such as the advanced age at diagnosis, high frequency of comorbidities and especially late diagnosis[4], which is still observed in majority of cases, despite advances in diagnosis, screening[5] and anti-tobacco laws[6].

Cytotoxic chemotherapy (CT) has been the backbone of systemic lung cancer treatment for many decades. However, the biological understanding of this disease and the advent of innovative genome sequencing technology have revolutionized the way we treat lung carcinoma – particularly adenocarcinoma. Those advances have made it possible to identify several therapeutic targets – so called actionable mutations, resulting in the introduction of new selective drugs associated with unprecedented tumor responses against rare and elusive non-small cell lung cancer (NSCLC) targets[7]. Thus, currently, an indispensable step in the treatment of NSCLC is the molecular subclassification of the disease which impact on both morbidity and mortality[1].

Nevertheless, despite important advances and of lessons that were learned, several challenges remains to be tackled prior to the expansion of the benefits of precision medicine in lung cancer[8]. Those challenges span from scientific and technical matters to the requirement of policy changes, regulatory adaptation and up to cost reduction accessibility and disparities issues[9].

This paper aims to discuss several aspects on how precision medicine positively impacted on lung cancer management and lessons learned. Additionally, we scoped future perspectives on lung cancer as technology advances.

Advances of precision medicine in lung cancer

Platinum-based CT was the standard of first-line NSCLC treatment up to the end of the 2000s, being associated with a median overall survival (OS) of 8 months[10]. Only in that decade, the need for better histological refinement for therapeutic choice was demonstrated based on clinical implications[11], such as a greater risk of hemorrhage in squamous histology with anti-angiogenic drugs[12] and a longer survival with pemetrexed in non-squamous histology[13].

From that moment on, a better comprehension of the molecular biology of lung cancer, aligned with progressive advances in genomic analyses techniques, have led to the identification of multiple tumor subtypes. The discovery of oncogenic factors potentially actionable by targeted drugs translated into the possibility of offering a personalized approach, significantly impacting survival rates for some subset of patients[14,15]. Precision medicine revolutionized lung cancer care, particularly non-squamous NSCLC (nsqNSCLC), and has achieved unprecedent response and survival rates[16–19].

A LONG WAY BETWEEN BIOMARKER IDENTIFICATION AND VALIDATION

The journey from discovery to clinical use of a biomarker is long and arduous. It must follow steps that influence the establishment of biomarkers in all applications throughout the course of the disease. The establishment of mutations in the epidermal growth factor receptor (*EGFR*) as the first biomarker in lung cancer has brought many lessons since the identification of this mutation back in 2004[20,21] until its' validation as a biomarker. Equivocal trial designs delayed the processes of understanding the role of a targeted drug and negatively influenced regulatory approvals, as trials were being conducted with unselected populations or with subjects selected only accordingly to specific phenotypes, instead of taking into account a specific biomarker[22]. Gefitinib was the first oral EGFR tyrosine kinase inhibitor (TKI) approved by the Unites States (U.S.) Food and Drug Administration (FDA) based in a phase II trial of NSCLC patients refractory to platinum- and docetaxel-based CT, back in 2003[23]. However, two years later, the approval was rescinded following the negative results of the phase III trial, despite an apparent benefit among non-smokers and patients of Asian origin[24].

Following the identification of somatic *EGFR* alterations in lung cancer several attempts were made to validate them as biomarkers. It was unclear which *EGFR* test would yield better outcomes with targeted-therapy: *EGFR* copy number by Fluorescence In Situ Hybridization (FISH), *EGFR* protein expression by immunohistochemistry (IHC), *EGFR* copy number by Polymerase Chain Reaction (PCR) or *EGFR* mutations by PCR[25]. Other molecular

features such as expression of the epithelial marker E-cadherin, or human epidermal growth factor receptor 2 (HER-2) and HER-3 amplification were also under investigation as predictors of EGFR-TKI response[26].

While FISH and IHC were initially considered as preferable testing approaches, PCR-based methods demonstrated controversial results[25,26]. Despite the identification of a higher frequency of *EGFR* mutations in non-smokers, females, and East-Asian patients with adenocarcinoma histology[27], besides the evidence between *EGFR*-mutations and sensitivity to targeted therapies[28–32], the association of EGFR-TKI with improved survival outcomes was yet to be clarified[32].

THE IRESSA PAN-ASIA STUDY AS A LANDMARK FOR CLINICAL ACTIONABILITY IN LUNG CANCER AND THE ERA OF ANTI-EGFR THERAPY

The phase III Iressa Pan-Asia Study (IPASS) trial selected patients in East Asia who had advanced pulmonary adenocarcinoma and who were non-smokers or former light smokers to receive gefitinib or doublet CT in the first-line setting[33]. The results were published in 2009, showing a favorable progression-free survival (PFS) with gefitinib in the intention-to-treat population. A pre-planned analysis of the study was carried out testing for mutations in the *EGFR* gene using PCR. Through this analysis, it was observed that only the subset of *EGFR*-mutated subjects benefited from gefitinib, while the wildtype subgroup achieved greater survival with the use of CT[33]. This clear correlation being proven, turned IPASS into a landmark for clinical actionability based on molecular testing in lung cancer, and established PCR-based *EGFR* testing as a response predictor method[34]. These findings can be considered the beginning of the precision medicine era in lung cancer.

Following IPASS, several first-line phase III studies selected patients with *EGFR*-mutated NSCLC and compared first- and second-generation EGFR-TKI with CT. With appropriate selection, all of them were positive for the primary endpoint PFS, although none of them demonstrated a formal gain in OS, due to the high crossover rate on trials[35–37]. This OS benefit was solely observed years later with the combination of gefitinib plus CT[38,39], and with the development of the third-generation EGFR-TKI osimertinib (FLAURA study)[16]. Recently, combinations of third-generation EGFR-TKI with CT or amivantamab (an *EGFR-MET* bispecific antibody), in first-line setting, have demonstrated increased PFS, however, at the expense of greater toxicity[40,41].

THE JOURNEY THROUGH THE ACTIONABILITY OF OTHER ONCOGENIC DRIVERS IN ADVANCED LUNG CANCER

Anaplastic lymphoma kinase (*ALK*) fusions were the second actionable target established in lung cancer. Compared to the decades invested in developing other kinase inhibitors, in 2011 crizonitib, a first-generation ALK-TKI, received accelerated approval by the FDA after a phase I trial showed promising outcomes in patients with NSCLC and *ALK* rearrangements[42,43]. Based on experience with EGFR-TKI, the repetition of costly mistakes was avoided in this setting and the investigation of ALK-TKI was immediately directed to this specific group of patients (i.e., *ALK*-rearranged NSCLC). Such decision ensured and speeded clinical development processes.

In 2013 the guideline from the College of American Pathologists, the International Association for the Study of Lung Cancer (IASLC), and Association for Molecular Pathology started recommending PCR-based *EGFR* testing and FISH-based *ALK* testing for all patients with advanced nsqNSCLC[44]. These recommendation was endorsed by American Society of Clinical Oncology (ASCO)[45]. The phase III PROFILE 1014 trial, published in 2014, confirmed the superiority of crizotinib over platinum-based CT for previously untreated advanced ALK-rearranged NSCLC[46].

Second- and third-generation ALK-TKI proved to be superior to first-generation crizotinib in terms of central nervous system activity and improvements in both PFS and OS, and are so far the standard of care for first-line treatment of advanced ALK-rearranged NSCLC[18,47,48]. No phase III studies have compared these drugs head-to-head[49].

With EGFR- and ALK-TKI paving the way for precision medicine in lung cancer, new molecular alterations, novel drugs and approvals were observed in the advanced scenario[50] - Figure 1. In 2016 crizotinib was approved by FDA for the treatment of proto-oncogene tyrosine-protein kinase-1 (*ROS1*) rearrangements[51], based on the results from a phase I trial[52]. In 2017 the first therapy for tumors with *BRAF* V600E mutation, dabrafenib plus trametinib, was approved by FDA[53] based on a phase II trial for previously treated[54] or untreated[55] patients.

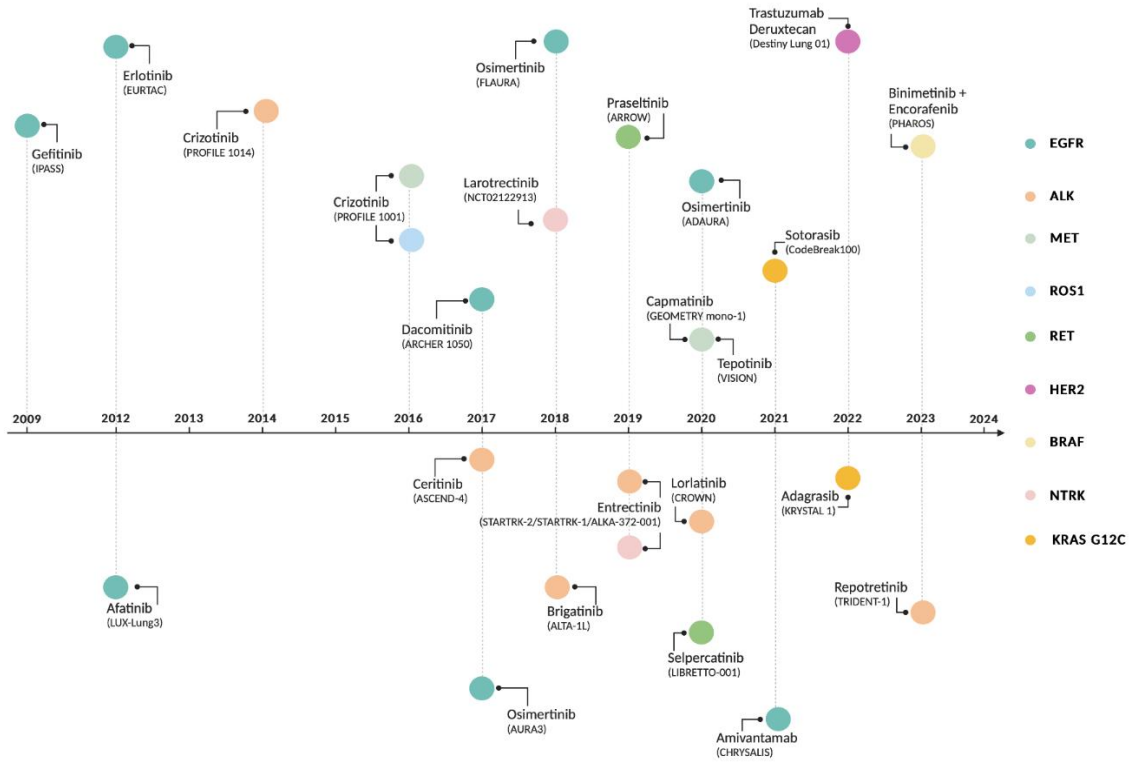

Figure 1 – Timeline for approved targeted therapies for non-small cell lung cancer

Alongside developments in precision medicine aimed for lung cancer care, first FDA agnostic therapeutical approval for advanced solid tumor harboring Neutrophic Tropomyosin Kinase Receptors (NTRK)-fusion first occurred in 2018, with larotrectinib[56].

More recently, new drugs have also been approved targeting *MET* exon 14 skipping alterations, Kirsten Rat Sarcoma viral oncogene homolog (*KRAS*) G12C mutation, *RET* fusions and *HER-2* mutations[57–60]. The approval of trastuzumab-deruxtecan (T-DXd) for *HER-2*-mutated NSCLC marks the beginning of the use of antibody-drug conjugates (ADCs) in lung cancer, a promising new class of drugs that has been widely explored[61].

Due to precision medicine, there are over 90 targeted therapies approved by the FDA for the treatment of eligible cancer patients, and the pharmaceutical pipeline for the development of novel agents involving biomarkers continues to increase[62]. A summary of approved targeted therapies for lung cancer based on reports of regulatory agencies from the U.S., European Union (EU) and Brazil are listed in Tables 1 and 2. With the incorporation of all these molecular-guided therapeutical options, an increasingly complex era in thoracic oncology has emerged, and decision-making regarding best treatment for advanced NSCLC relies on a much greater number of variables than before.

Table 1 – Approved targeted therapies for EGFR and ALK mutations for non-small cell lung cancer based on regulatory agencies report.

	Study/Year of publication	FDA approval		Year	EMA approval		Year	ANVISA approval		Year
		Yes	No		Yes	No		Yes	No	
***EGFR* – exon 19 deletion/L858R mutation**										
First generation										
Erlotinib	First line: EURTAC, 2012[36]	X		2013	X		2011	X		2012
Gefitinib	First line: IPASS, 2009[33]	X		2015	X		2018	X		2011
Second generation										
Afatinib	First line: LUX-Lung3, 2012[63]	X		2013	X		2013	X		2016
Dacomitinib	First line: ARCHER 1050, 2017[64]	X		2018	X		2019		X	
Third generation										
Osimertinib	First line: FLAURA, 2018[65]	X		2018	X		2018	X		2018
	Second line or more: AURA3, 2017[66]	X		2015*	X		2016	X		2016
	Adjuvant: ADAURA, 2020[67]	X		2020	X		2021	X		2021
***EGFR* – exon 20 mutation**										
Amivantamab	Second line: CHRYSALIS, 2021[68]	X		2021	X		2021	X		2021
ALK										
First generation										
Crizotinib	First line: Profile 1014, 2014[69]	X		2011*	X		2015	X		2016
Second generation										
Alectinib	First line: ALEX trial, 2017[70]	X		2017	X		2017	X		2019
Brigatinib	First line: ALTA-1L, 2018[71]	X		2017	X		2018			
Ceritinib	First line: ASCEND-4, 2017[72]	X		2017	X		2017			
Third generation										
Lorlatinib	First line: CROWN, 2020[73]	X		2021	X		2021	X		2021

Abbreviations: NSCLC – non-small cell lung cancer; FDA – Food and Drug Administration; EMA – European Medicines Agency; ANVISA –Brazilian Health Regulatory Agency; EGFR – epidermal growth factor receptor; ALK – anaplastic lymphoma kinase.

Table 2 – Approved targeted therapies for rare mutations for non-small cell lung cancer based on regulatory agencies report.

	Study/Year of publication	FDA approval		Year	EMA approval		Year	ANVISA approval		Year
		Yes	No		Yes	No		Yes	No	
ROS1										
Crizotinib	PROFILE 1001, 2016[74]	X		2016	X		2016	X		2018
Repotretinib	TRIDENT-1, 2023[75]	X		2023		X			X	
Entrectinib	STARTRK-2/STARTRK-1/ALKA-372-001, 2019[76,77]	X		2019	X		2020		X	
***KRAS* G12C**										
Sotorasib	Second line: CodeBreak100, 2021[78]	X		2021	X		2022	X		2022
Adagrasib	Second line: KRYSTAL-1, 2022[79]	X		2022		X			X	
RET										
Pralsetinib	Second line: ARROW, 2021[80]	X		2020*	X		2021		X	
Selpercatinib	Second line: LIBRETTO-001, 2020[81]	X		2020*		X			X	
BRAF										
Binimetinib + Encorafenib	PHAROS, 2023[82]	X		2023		X			X	
Dabrafenib + Trametinib	NCT01336634, 2017[55]	X		2017	X		2017	X		2018
MET – exon 14 skipping										
Crizotinib	PROFILE 1001, 2016[83]	X		2018		X			X	
Capmatinib	GEOMETRY mono-1, 2020[84]	X		2020	X		2022	X		2021
Tepotinib	VISION, 2020[85]	X		2021*	X		2022	X		2021
NTRK										
Entrectinib	STARTRK-2/STARTRK-1/ALKA-372-001, 2019[86]	X		2019	X		2020		X	
Larotrectinib	NCT02122913, 2018[87]	X		2018*						
HER-2/ ADC										
Trastuzumab Deruxtecan	Destiny Lung01, 2022[88]	X		2022*	X			X		

Abbreviations: NSCLC – non-small cell lung cancer; FDA – Food and Drug Administration; EMA – European Medicines Agency; ANVISA –Brazilian Health Regulatory Agency; ROS1 – proto-oncogene tyrosine-protein kinase-1; KRAS – Kirsten Rat Sarcoma viral oncogene homolog; MET – mesenchymal epithelial transition; NTRK – neurotrophic tropomyosin kinase receptors; ADC – antibody drug conjugate

ADVANCES IN MOLECULAR TESTING METHODOLOGIES

The recent advances in testing methodologies, software and bioinformatics tools for data analysis have been crucial for the characterization of multiple molecular subtypes of lung cancer and the development of precision medicine. After PCR-based DNA sequencing technologies, such as Sanger method, have been developed in the 1970s, the so called Next-Generation Sequencing (NGS) emerged in the last decades and allowed a broader analysis of DNA and RNA structures[89]. The capacity of the technology to generate a huge amount of biological information required computational and human developments for data analysis[90]. FDA approved the first NGS test for detecting multiple biomarkers from a single sample of lung cancer in 2017[53], facilitating allocation of advanced NSCLC patients into a guided-treatment based on the results from a single test[91]. Advances in minimally invasive procedures technologies led to an access of smaller tissue fragments. However, pre-analytical sample preparation is often not carried out properly and inadequate sample quantity or quality are some of the challenges for sequential testing of multiple genes mutations using older testing methods[92]. As technology advanced the development and applicability of sequencing methods from a single-cell analysis also occured[93,94].

Although cost-effectiveness studies favored NGS testing before deciding on first-line treatment for advanced NSCLC[95,96], costs with novel testing methodologies, turnaround time, and access restriction to some targeted therapies can still make it difficult to completely abandon older testing methods. Also, genomic testing protocols may vary geographically. Some obstacles such as heterogeneity to healthcare access, absence of quality control guidelines and policies for molecular testing, issues involving payment and reimbursement represent real challenges in low and middle-income countries (LMICs)[97]. In this way, specific tests based in RT-PCR, IHC and FISH can still be very useful for detecting the most frequent molecular alterations, with a reasonable time and cost[89].

The process of molecular analysis in circulating cell-free tumor DNA, typically from peripheral blood sample, is known as liquid biopsy. The test specificity to find driver mutations in plasma genotyping is high, but its' sensitivity of the method ranges between 60% to 80%[98]. Liquid biopsy NGS usage for detecting actionable *EGFR* mutations in NSCLC was first approved by FDA in 2020[99]. Even though the technology has been extensively studied as a minimally invasive complementary or alternative method to tissue NGS, this was the first application for liquid biopsy in clinical practice, and it can be helpful for diagnostic purposes, for monitoring the effectiveness of therapies and for identifying acquired resistance mechanisms[100,101].

PRECISION MEDICINE APPLICATION IN RELAPSED OR PROGRESSIVE DISEASE

Tailored treatment decisions have also been achieved in relapsed or progressive disease. Sequential molecular analyses (tissue or blood) of relapsed or progressive NSCLC can provide important insights into biomarker profiling changes and identify new actionable genetic alterations[102]. For instance, testing for *EGFR* T790M mutation after treatment failure with first- or second-generation EGFR-TKI became a standard recommendation since this mutation is recognized as the main mechanism of resistance to these drugs. Moreover, such mutation is sensitive to third-generation EGFR-TKI[103].

Given the higher sensitivity and specificity of genomic testing in tumor tissue samplings, this method still is considered the preferential approach for molecular analysis. However, liquid biopsy has been a plausible option in cases of recurrent or progressive disease in patients not suitable for tissue biopsy, minimizing complications due to new tumor biopsies and being more comfortable for patients with poor performance statuses. Furthermore, liquid biopsy is a minimally invasive, repeatable, easily acceptable, and less expensive procedure. It can also reveal tumor heterogeneity and longitudinal changes[104]. Nonetheless, liquid biopsy has relevant limitations such as the difficulty of identifying histological transformations, gene fusions or amplifications, and has low sensitivity in patients with low tumor burden. It can also potentially classify clonal hematopoiesis mutations as tumor-derived mutations and lead to inappropriate therapeutic management[101,105].

Thus, ideally, in cases of disease progression, liquid biopsy in parallel to tissue biopsy could identify the global molecular portrait of the tumor, which would allow the rapid detection of resistance mechanisms and, consequently, a rapid adaptation of the next line of treatment[8,106]

FROM ADVANCED DISEASE TO EARLIER STAGES

Precision medicine is progressively gaining a role in the treatment of lung cancer at earlier stages. After some trials failed to demonstrate OS benefit with first-generation EGFR-TKI in the adjuvant setting[107], the results from the phase III ADAURA trial showed a notable disease-free survival and OS benefit with the adjuvant use of osimertinib compared to

placebo, among patients with resected *EGFR*-positive stage IB to IIIA NSCLC (per 7th edition classification of American Joint Committee on Cancer [AJCC])[67,108]. Therefore, FDA approved osimertinib for adjuvant therapy in 2020[109].

Recently, the adjuvant use of second-generation ALK-TKI alectinib for resected stage IB to IIIA (AJCC 7th edition) *ALK*-rearranged NSCLC was correlated to disease-free survival improvement when compared to adjuvant CT in the phase III ALINA trial[110].

Other phase III trials are evaluating targeted-therapies in both neoadjuvant and adjuvant settings for resectable early-stage NSCLC[107,111]. Omission of adjuvant CT and the proposed duration of adjuvant targeted therapy varies among these trials and remain grounds for discussion[111]. Some of these studies evaluate the adjuvant use of TKI in rare molecular alterations for which the benefit of targeted therapy has already been unquestionably demonstrated in the metastatic setting[81,112,113]. After the proof of concept of the ADAURA study[114] and considering the cost of trials and recruitment time, the real need for phase III trials to prove the benefit of these adjuvant therapies must at least be questioned.

Challenges

COST EFFECTIVENESS AND ACCESSIBILITY

The integration of precision medicine technology into health care has undoubtedly improved lung cancer outcomes, but it also led to a surge in treatment costs, creating concerns regarding affordability of equitable care[115,116]. The lack of comprehensive studies has left cost-effectiveness of precision medicine in lung cancer unclear, and there is limited knowledge about it overall net benefit[115]. Even though the use of NGS for adenocarcinoma histology allowed more accurate gene diagnosis, it did not consider cost-effectiveness or quality-adjusted life-years when compared to single genomic tests models in the context of supplementary health system in Brazil[117,118]. Despite the efficacy of osimertinib in the first-line treatment of *EGFR* mutated NSCLC patients, the drug was not considered cost-effective either in the U.S. and Brazil[119]. In contrast, a study showed alectinib cost-effectiveness for ALK mutated patients treatment in some high income countries (HICs)[120,121].

In scenarios where genetic testing is applied to many patients to identify only a few individuals with a rare mutation responsive to a specific treatment, the overall benefit may be diluted[115]. To optimize cost-effectiveness, precision medicine application can be strategically used for early intervention over treatment stratification in advanced diseases, which can reduce long-terms costs associated with therapy[122].

A systematic review showed a wide price variation on cancer drugs price between countries, being less affordable on LMICs than HICs[123]. A Brazilian study showed the contrast between the standard of care treatment cost for lung cancer and the amount reimbursed by public health care, indicating a gap of 9,118%[124].

A pricing policy and actively encouragement the development and approval of generics and biosimilars may be a valid path to ensure global affordability, facilitate access to innovative and effective treatments, therefore, improving the quality of lung cancer care and patient outcomes[118,125,126].

EDUCATION: MULTIDISCIPLINARY TUMOR BOARD AND MOLECULAR TUMOR BOARD

Multidisciplinary Tumor Board (MTB) is defined as a group that regularly gather to discuss a series of patients, aiming to reach a definitive diagnosis, stage and treatment plan[127,128]. MTB is composed by several different professionals and specialties, and aims to ensure attention to all aspects of cancer care, including rehabilitation, psychosocial needs and long-term care[127,128].

Implementation and maintenance of regular MTB in some institutions remains a challenge due to a lack of funding and structures that support gatherings, team adherence with balanced representativeness, and the need of an effective leadership to moderate cases and promote discussion[128]. MTBs are an essential tool for a high-quality and patient-centered oncology practice that supports continuous learning and improvement of all team members[127–129].

With the advent of molecular profiling as part of the evaluation of patients with NSCLC, a novel challenge to comprehend complex genomic data and its application on clinical practice was introduced. Molecular tumor board facilitates the delivery of precision oncology, translate genomic test results into therapeutic strategies, identify new use for approved drugs beyond their original indication and can aid to capture case for clinical trials[130,131]. However, its' sustainability relies on securing funding, resources, and expertise to provide access to all community.

THE IDEAL BIOMARKERS FOR IMMUNE CHECKPOINT INHIBITORS

Parallel to advances in targeted therapies, advances also occurred in the immune-oncology (IO) field. The immune checkpoint inhibitors (ICI) approved for lung cancer treatment may function as a "targeted therapy" even though there's no ideal target per se. Basically, the only predictive biomarker currently available is the programmed death-ligand 1 (PD-L1) score[132]. Despite the high predictive value of PD-L1 expression and response, many questions still need to be clarified. PD-L1 expression is heterogeneous and may vary between tumor sites (primary and metastasis), besides the predictive value is different according to histology subtypes. Additionally, it has been observed objective response in patients with PD-L1 negative tumors, suggesting that other markers may influence the response to immunotherapy, such as TMB, presence of concurrent mutations and tumor microenvironment[133,134]. Other important limitations and multiple unsolved issues such as the lack of validation for immunohistochemistry laboratory-developed tests, the use of different staining platforms and antibodies, thresholds values used for PD-L1-positivity, the source and timing for sample collection and the type of cells in which PD-L1 is assessed (tumor versus immune cells)[132]. With the lack of an ideal biomarker, selection bias is inevitable, leading to clinical benefit in only a small portion of treated patients[133–135].

Regarding TMB, several studies have demonstrated its' predictive value for immunotherapy, suggesting that a high TMB score is associated with better overall rate response (ORR) and longer survival[134,136,137]. Nonetheless, there are limitations for the use of TMB as a predictive biomarker. Therefore, alternatives have been studied such as the application of neoantigens originated from somatic mutations by the antitumor response of T cells[138–141]. The predictive role of PD-L1 in combination with TMB has been evaluated before in NSCLC. While they may work as independent predictors of ICI efficacy and might not correlate with each other, those with high TMB and PD-L1 ≥ 1% may have higher durable clinical benefits than other subsets of patients[142].

In recent years, artificial intelligence (AI) is being studied to help model and predict medical information. A growing number of studies have combined radiology, pathology, genomics, proteomics data to predict the expression levels of PD-L1, tumor TMB and tumor microenvironment in cancer patients or predict the likelihood of immunotherapy benefits and side effects[143,144].

As for most common target mutations for NSCLC, the efficacy of ICI in those with targetable drivers is largely unknown. Some mutations such as BRAF, cMET, and KRAS altered NSCLC appeared to be like what had been observed in the non-selected NSCLC groups, however, for EGFR, ALK and RET the ORR are much lower[145]. Therefore, the role of ICI for patients with actionable drivers remains controversial. Most available data for this specific groups derives from either subgroup analysis of clinical trials, small phase I or II noncontrolled trials with combination regimens (generally including a targeted TKI as backbone), or retrospective analysis from real clinical practice[146].

HURDLES TO OVERCOME IN SQUAMOUS NON-SMALL CELL LUNG CANCER AND SMALL-CELL LUNG CANCER

The role of molecular targeted therapy in squamous NSCLC (sqNSCLC) is very limited and has become a major focus in current research[147], including not only the identification of new tumor biomarkers, but also novel targets to specific drug therapy[148]. Besides PD-L1 no fundamental markers have been described for these patients in which directed therapy currently exits for a non-squamous histology[149]. *EGFR* mutations have a prevalence of 3 % to 18% among patients with sqNSCLC, and response rates ranging from 25% to 49% with median PFS ranging from 1 to 5 months in some cohorts[150]. *ALK* rearrangements have been reported in a frequency of 1% to 2.5% among SCC patients, and the utility of ALK-TKI remains controversial since the duration of benefit is shorter than patients with non-squamous histology[151]. Additionally, some specialists advocate that NGS may be fully applied to all NSCLC[148], since even though a targeted oncogene is less frequent identified with the test in this setting, other mutations, such as KMT2D, PIK3CA and NFE2L2 may serve as pivotal factors for future trials[149].

Regarding small-cell lung cancer (SCLC), multiple chromosomal aberrations, loss of tumor suppressor genes (i.e., *RB1* and *TP53*), and other mutations such as PTEN, PI3KCA, *EGFR*, *KRAS*, and NF1 can be found. Nonetheless, unlike NSCLC, being able to identify actionable targets in SCLC has been challenging. For instance, *ALK* mutations are extremely rare and cited in a few case reports[152], as for *EGFR* mutations, the most related to SCLC occurs after a NSCLC transformation[153]. Furthermore, despite several additional attempts to use other inhibitors such as mTOR, cKIT, MET, and BCL-2, which all failed to prove efficacy against SCLC[154]. A new paradigm on SCLC is a recent stratification of this tumor according to the e

expression levels of achaete-scute homolog 1 (ASCL1), neurogenic differentiation factor 1 (NEUROD1), and POU class 2 homeobox 3 (POU2F3) on IHC, and these three molecules may drive the biological behavior of SCLC[155]. Based on that classification, SCLC now may be divided into four subtypes, i.e., SCLC-A (ASCL1-dominant), SCLC-N (NEUROD1-dominant), SCLC-P (POU2F3-dominant), and SCLC-I (triple negative or SCLC-infamed). However, although this became a new spotlight for SCLC, precision medicine has not evolved enough to provide new potential targets[155], and ideal biomarkers are virtually non-existing for this type of lung cancer. Besides PD-L1 does not play the same role as it does in NSCLC[156]. In a much slower pace than NSCLC, recently, the implementation of tarlatamab, a bispecific T-cell engager molecule, that binds both DLL3 and CD3 with CT for patients who failed first line of treatment with CT + IO[157,158] became a promising alternative to standard second-line therapy.

THE OPTIMAL TREATMENT STRATEGY AND SUBSEQUENT THERAPIES

A broad range of recent treatment options for the same clinical scenario has posed a challenge to thoracic oncologists to pick the best, however the lack of studies comparing different first-line treatments for NSCLC poses a challenge in determining an optimal therapy approach. The absence of such comparative data makes it difficult to definitively determine the most suitable choice.

Pharmaceutical industry tends to decline head-to-head comparisons to avoid jeopardizing its market share by unfavorable results[159]. Industry trials were more likely to perform noninferiority/equivalence design since is less risk and still enough to support product approval[159,160]. Most of the industry-sponsored randomized research is sponsored by a single company, when comparing two drug interventions. In such case, it is common for the industry seeking to establish the superiority or non-inferiority of its new agent to sponsor the trials. This practice raises question about potential biases and conflicts of interest[160]. Regulatory agencies should encourage head-to-head trials for a more comprehensive understanding of treatment options and promoting evidence-based medicine[159].

Major improvements arose on NSCLC treatment as a first-line option. Regardless of these breakthroughs, disease progression will occur at some point during its' natural course[161], and contemporary research are trying to stablish what is the next step. Subsequent management decisions are based on tumor and patient characteristics, and modalities of previous treatment[162]. Personalized medicine has become fundamental to understanding the etiological diversity of lung cancer and can unravel resistance mechanisms and development of studies focusing on combination therapies[163]. Some gaps in the NSCLC treatment strategy that still demand focused attention like determining drugs optimal dosage and sequencing, when use associations, and the ideal duration of treatment[162].

For patients with adenocarcinoma, ADCs are the novelty in cancer management. The combination of specific monoclonal antibodies (mAbs) with a cytotoxic effect of a conjugated payload proofed to be effective in previous studies[164]. In this setting, several ADCs are being developed and studied in different combinations in both first- and second-line treatment[161], such as HER-2, HER-3, trophoblast cell surface antigen 2 (TROP2), c-MET, carcinoembryonic antigen–related cell adhesion molecule 5 (CEACAM5), and B7-H3[165].

Future perspectives

The present is an exciting time for lung cancer treatment. In recent years, precision medicine and the gains it generates have drastically improved outcomes related to this disease. However, these improvements are accompanied by a need for data to inform clinical decisions, and therefore a need to be able to make sense of large volumes of data throughout a hypothetical patients' treatment course. Thus, the comprehensive field of AI offers a promising path to improving all aspects of managing this data and based on it, defining approaches.

With the advancement of technology, there has been an explosion in the generation and collection of large-scale health data, leading to the formation of large data sets, known as big data.[166]. AI, in combination with big data analytics, has the potential to extract valuable insights and hidden patterns from these large data sets. This tool is already known to be resourceful for lung cancer diagnosis, screening, and assisting pathology reports[143,144,167]. With proper radiomics AI may predict prognostic features such as tumor responses to treatment, the occurrence of metastasis[168] and may assist physicians on how to decide which treatment may fit better to each patient based on molecular profiling. Additionally, the combination of AI and NGS results may lead to identification of tumor biomarkers and its' implications on cancer prognosis. However, the current big data technology does not combine data from multiple fields for big data's fully potential, since there're some issues such as poor data quality, unstructured databases, inadequate analytics, and lack of

delivery. Here lies the need of reliable databases to better understand cancer dynamics[166].

Soon the identification of potential biomarkers in which efficient targeted drugs will become available will guide how thoracic oncologists will treat patients irrespectively of the line of therapy[169]. The early detection of biomarker-driven biology helps to obtain a greater benefit for a selected population and can reduce the required time for drug approval[169]. For that matter, another future perspective is related to lung cancer trial designs. Currently, one of the most pressing needs is a call to action to establish the anticipated framework and path forward for next generation clinical trials[170]. Historically, pharmaceutic development in oncology comprises a series of stages from phase I through phase IV clinical trials[171]. Methodological advancements in adaptive clinical trial, as basket and umbrella trials, will help catalyze the adoption of precision medicine and oncology into clinical practice and an educational effort must be made regarding its' advantages and disadvantages[172]. In summary, perhaps phase III trials will no longer be required to all potential targets and drug approval.

Finally, in vitro experiments might represent a novel pre-clinical example of precision medicine. It is already known that circulating tumor cells and circulating tumor DNA (ctDNA) complement each other on novel approaches regarding tumor heterogeneity, with a potential do predict treatment responses, prognosis[4], monitoring disease burden[173], and risk of relapse[174]. In that matter, new pre-clinical in vitro analysis may show that acquired resistance can emerge before the drug exposure occurs, suggesting that some cells are in any case resistant to treatment[4], yielding an understanding that access tumor's microenvironment in this frontier has the potential to optimize more effective immunology-based precision therapies[4]. In sum, there is hope the optimal use of AI will move precision oncology to a new paradigm with a more efficient journey from biomarker identification and validation, trial design, drug approval and ultimately better and more affordable patient tailored treatments.

Conclusion

Precision medicine had a massive impact on lung cancer management over the past decades. The acquired information derived from the available technology allowed thoracic oncologists to improve patient care and optimize outcomes. Yet, appointed hurdles on daily practice are no longer restricted solely to diagnostic tools, they escalated to applicability and accessibility of these tests, and further discussion to tackle this issue must be properly conducted. As technologies such as AI continue to evolve, our main challenge is to make precision medicine more efficient and cost effective for all lung cancer patients. To achieve that, all the stakeholders namely scientists, physicians, patient advocacy and policy makers must work together.

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