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Genomics and the treatment of lung adenocarcinoma: A review for clinicians.

Tiago Elias Heinen [1,2]; Juliano Cé Coelho [1,2]; Rodrigo Perez Pereira [1,2]; Elvis Pellin Cassol [1]; Gabriela Teixeira Andrade [1,2]; Andréa Baldasso Zanon [1]; Gabriela Gatto [1]; Pedro Emanuel Rubini Liedke [1,2]; Sérgio Jobim de Azevedo [1,2,3]

1. Unidade de Pesquisa Clínica em Oncologia (UPCO) – Hospital de Clínicas de Porto Alegre.
2. Grupo Oncoclinicas de Porto Alegre.
3. Departamento de Medicina Interna, Faculdade de Medicina da Universidade Federal do Rio Grande do Sul.

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ABSTRACT

Lung cancer remains a leading cause of cancer-related mortality worldwide. Despite improvements in treatments over the past decade, advanced non-small cell lung cancer remains an incurable disease. The scenario, however, has improved for patients with site-directed mutations. Targeted therapy for lung cancer refers to the use of drugs that specifically attack molecular or genetic alterations present in tumor cells. This type of approach has revolutionized the treatment of non-small cell lung cancer, especially adenocarcinomas.

The identification of specific mutations, such as mutations in the epidermal growth factor receptor and rearrangements in anaplastic lymphoma kinase, has allowed the development of tyrosine kinase inhibitors, which significantly improves clinical outcomes compared to traditional chemotherapy, in addition to being a better tolerated treatment. Other targets have already been identified and, today, the broad search for molecular targets is part of the initial evaluation of patients with advanced adenocarcinoma.

We live in a time of continuous evolution in targeted therapy and with better understanding of the mechanisms of resistance to treatments, which has been explored in recent clinical trials. Previously a fatal disease, today, in a considerable number of cases, we are reaching chronicity. This is why the subject should be on the agenda not only for oncologists, but for clinicians in general. The objective of this review is to address the main targets related to the treatment of lung adenocarcinoma and the results of effective inhibition, discussing both classical therapies and new therapeutic approaches.

Introduction

Lung cancer is the leading cause of cancer-specific death worldwide, with an estimated 2.4 million new cases in 2022, unfortunately still accompanied by 1.8 million deaths[1]. Pathological classification indicates that 85% of lung cancers are non-small cell lung cancers (NSCLC), most of which are diagnosed as metastatic or locally advanced disease. Until the turn of the century, palliative treatment consisted mainly of cytotoxic chemotherapy, resulting in the disappointing outcome of a median overall survival of 12 months [2]. Nowadays, this scenario has been altered dramatically with the availability of biomarkers to select patients for targeted and immunotherapy-based treatments[3].

For lung cancer patients with adenocarcinoma histology (which accounts for 50-60% of NSCLC cases), the prevalence of targetable driver mutations was 54% in a nationwide French study. However, this prevalence increased to 78% when focusing on the non-smoking population. In this trial, over 16,000 NSCLC patients underwent molecular profiling, with half receiving targeted therapy in the first-line setting. When a genetic alteration was detected, the median overall survival (OS) was 4.7 months longer compared to when no genetic alteration was present, suggesting a possible prognostic advantage or a significant change in management for these patients[4].

Today, molecular classification of NSCLC has become essential in defining the treatment strategy for metastatic and locally advanced disease. Recent evidence also points to a potential benefit in the adjuvant and neoadjuvant settings. Actionable biological targets in the treatment of lung adenocarcinoma include mutations in the gene encoding the epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), c-ROS oncogene 1 (*ROS1*), v-Raf murine sarcoma viral oncogene homolog B (BRAF) V600E mutation, neurotrophic receptor tyrosine kinase (NTRK) fusions and, more recently, rearranged during transfection (RET) fusions, mesenchymal-to-epithelial transition (MET) mutations, human epidermal growth factor receptor 2 (HER2), and kirsten rat sarcoma viral oncogene homolog (KRAS)[5]. To identify these targets, commonly used techniques include fluorescence in situ hybridization (FISH), immunohistochemistry, DNA sequencing, DNA allele-specific testing, and DNA and RNA next-generation sequencing (NGS). Liquid biopsies can identify these alterations through blood-based tests, although they have a higher risk of yielding false-negative results compared to traditional biopsies[6].

Over the past two decades, various target therapies have been approved for the treatment of advanced lung adenocarcinoma, demonstrating better survival outcomes compared to traditional chemotherapy. Additionally, targeted therapy is generally less toxic than chemotherapy, ensuring a better quality of life. Here we review these molecularly targeted drugs used to NSCLC with improvement in survival endpoints.

Epidermal growth factor receptor (EGFR)

The Epidermal Growth Factor Receptor (EGFR, also known as ErbB1 or HER-1) belongs to the receptor tyrosine kinase (RTK) superfamily, which consists of three other members: ErbB2/Neu/HER-2, ErbB3/HER-3 and ErbB4/HER-4[7].

Historically, EGFR derives its name from studies in the 1960s, when its ligand, EGF (epidermal growth factor), was discovered as a protein that stimulated the proliferation of epithelial cells[8]. It was only a decade later that the receptor itself was identified, and today, seven ligands are known to have the potential to activate it[9,10]. EGFR ligands are high-affinity and structurally similar proteins, including EGF, transforming growth factor-α (TGF-α), heparin-binding EGF (HB-EGF) and b-cellulin (BTC), and low-affinity ligands such as amphiregulin (AR), epiregulin (EREG) and epigen (EPGN)[11,12]. When activated by one of its ligands, the intracellular kinase domain will activate second messengers to propagate the message to the cell nucleus[13].

These pathways, from a biological point of view, play a fundamental role during embryogenesis and in healthy adult tissues, being involved in the growth, differentiation, and maintenance of epithelial cells and, consequently, organs [12,14]. In the same way, however, the EGFR pathway can be the cause of the emergence of neoplasms, and is therefore considered an oncogenic driver[15]. In lung cancer, for example, EGFR can initiate tumorigenesis by activating pro-survival and anti-apoptotic cellular responses, including increased proliferation, motility, angiogenesis, vascular mimicry, and invasiveness[16].

Lung cancer is characterized by the accumulation of multiple genetic and epigenetic alterations, including somatic mutations, gene copy number gain, which leads to the activation of oncogenes or inactivation of tumor suppressor genes[17]. Among these alterations, the dysregulation of EGFR signaling stands out[15]. Mutations in the EGFR gene are observed in approximately 10–30% of NSCLC adenocarcinomas in Caucasians. In Asians, however, these numbers reach 60%. These mutations are known to promote tumorigenesis and are mainly seen in patients who have never smoked, although they can also appear in smokers or ex-smokers. There are several types of EGFR mutations, which confer different levels of sensitivity to different tyrosine kinase inhibitors (TKIs)[18].

The so-called classical EGFR mutations include the deletion of exon 19 (p. E746–A750del) and the L858R point mutation of exon 21 (del19 or L858R), which are also the most common, accounting for approximately 80–85% of mutations in this receptor[17]. These alterations can be identified mainly by polymerase chain reaction (PCR) methods or, more recently, by next-generation sequencing platforms (NGS), which increases the number of genes that can be analyzed and, consequently, the sensitivity of the test. Furthermore, today we have liquid biopsy, in which a simple peripheral blood puncture can provide material to evaluate circulating tumor DNA (ctDNA), facilitating the analysis of mutations[19].

Nowadays, EGFR tyrosine kinase inhibitors represent the first-line treatment and targeted therapy for patients with metastatic NSCLC harboring EGFR mutations

(Ex19Del and L858R)[17]. This success story began about two decades ago, when the first-generation TKIs, gefitinib and erlotinib, showed dramatic response potential in specific patient groups, such as Asian women, young people, and nonsmokers [20,21].

The classic IPASS study demonstrated the importance of EGFR detection. In this study, 1,217 Asian patients who were non-smokers or former light smokers were randomized to receive first-line treatment with gefitinib (250 mg orally daily) versus chemotherapy with carboplatin and paclitaxel. Progression free survival (PFS) was superior in the gefitinib group (HR=0.74; 95% CI: 0.65-0.85; p<0.001). Subgroup analysis, however, showed that the increase in PFS came at the expense of the 261 patients with EGFR mutation (9.6 versus 6.3 months for gefitinib versus carboplatin and paclitaxel; p<0.001). On the other hand, patients without the mutation had a PFS of 1.5 months compared to 5.5 months in the chemotherapy group. Overall survival was similar between groups, but treatment with TKI had a much more favorable toxicity profile compared to chemotherapy[18]. This study highlighted the importance of testing patients with lung adenocarcinoma for EGFR mutations in order to improve selection and provide personalized treatment.

Corroborating these data, other studies, such as WJTOG3405, a Japanese phase 3 trial, selected patients with EGFR mutation to receive gefitinib (250 mg/day orally; n=88) or cisplatin plus docetaxel (n=89). The primary endpoint was PFS, with a median of 9.2 months versus 6.3 months (HR 0.489; 95% CI 0.336-0.710; p<0.0001), favoring the TKI. As in the IPASS study, the toxicity profile of the TKI was better[21].

Erlotinib, another first-generation EGFR inhibitor, also showed a superior PFS to chemotherapy in the Chinese OPTIMAL study, reaching a median of 13.1 months versus 4.6 months in those who received chemotherapy[22]. Similarly, the European EUTARC study showed that Erlotinib is superior to chemotherapy in terms of PFS when offered to patients with classic EGFR mutations, reaching a PFS of 9.7 months versus 5.2 months[23]. Erlotinib was also evaluated in a Spanish study in EGFR mutation carriers (for first- or second-line treatment) and demonstrated high response rates (71%), median PFS (14 months) and median OS (27 months) with no differences between those who received the tyrosine kinase inhibitor as first or second-line[24].

One of the great advantages of using TKIs for the treatment of lung cancer is their favorable toxicity profile compared to chemotherapy, which consequently allows the use of these drugs in fragile patients. To corroborate this idea, a Japanese phase II study used gefitinib in the first line therapy in elderly patients and/or those with a low performance status (including ECOG 3 and 4). The response rate and median OS were 66% and 17.8 months, respectively. There was an improvement in the ECOG performance status ≥ 3 to ≤ 1 in 68% of cases [25].

Among the second-generation inhibitors, such as Afatinib, the Lux Lung 3 study evaluated its efficacy against cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. Median PFS was 11.1 months for afatinib and 6.9 months for chemotherapy, which was statistically significant[26].

Third-generation TKIs have been compared with previous-generation TKIs. The phase III FLAURA study demonstrated the superiority, in first line, of osimertinib over erlotinib or gefitinib in 556 patients with classical sensitivity mutations (del19 or L858R), with a median PFS of 18.9 versus. 10.2 months (HR=0.46; 95% CI: 0.37-0.57; p<0.0001) and objective response rate of 80% versus 76%. Results were also similar for patients with central nervous system (CNS) metastases. Adverse events of grade 3 or higher were less frequent with osimertinib than with standard EGFR-TKIs (34% versus 45%)[27]. More recently, OS data were presented, with a median of 38.6 versus 31.8 months, favoring osimertinib (HR=0.799; 95% CI: 0.641-0.997; p=0.0462), despite the crossover of approximately one quarter of patients in the control arm. At 3 years, 79 of 279 patients (28%) in the osimertinib group and 26 of 277 (9%) in the comparator group were continuing on the trial regimen[28]. Due to data on lower toxicity, better control of CNS disease, and increased OS compared to previous generation TKIs, osimertinib, a third generation TKI, is currently considered the first-line treatment for patients with NSCLC harboring classical EGFR mutation.

Another strategy used in the first line is the combination of TKIs with chemotherapy. A Japanese phase III study evaluated the combination of gefitinib with carboplatin and pemetrexed in patients with EGFR mutation (del19 or L858R) versus gefitinib monotherapy. Median PFS and OS were 20.9 and 52.2 versus 11.2 and 20.7 months in the combination and gefitinib monotherapy arms, respectively. Overall response rate (ORR) was also superior in the combination, reaching an incredible 84% versus 67.4%. The rate of grade ≥ 3 adverse events, such as hematologic toxicity, was higher in the combination group, however, no difference was found in the assessment of quality of life 29 . Similarly, the FLAURA 2 study randomized 557 patients with classical EGFR mutations (del19 or L858R),1:1, to receive osimertinib 80 mg/day orally alone versus the same dose of osimertinib combined with cisplatin or carboplatin-based chemotherapy plus pemetrexed, every 3 weeks, for 4 cycles, followed by maintenance pemetrexed with osimertinib. The combination was superior to osimertinib alone in its primary endpoint, with a 3-year PFS of 57% versus 41% (HR=0.62; 95% CI: 0.49-0.79; p<0.0001). In absolute terms, the median PFS in the combination was 25.5 months versus 16.7 months for osimertinib alone, also a significant finding. The combination was also better in patients with brain metastases, achieving a median PFS of 24.9 versus 13.8 months, in addition to a higher ORR of 83% versus 76% when analyzing all patients. As expected, the combination group presented greater toxicity, but effects already known in relation to chemotherapy[30]. Both studies cited become important, since the TKI + chemotherapy combination becomes interesting in specific groups of patients, such as patients with good performance status, who have a high volume of disease or even brain metastases.

In 2023, the MARIPOSA trial was presented at European Society for Medical Oncology congress (ESMO), which evaluated the combination of amivantamab (a bispecific

epidermal growth factor (EGF) receptor-directed and mesenchymal–epithelial transition (MET) receptor-directed antibody) combined with lazertinib (third-generation anti-EGFR) versus lazertinib monotherapy versus osimertinib monotherapy for patients with previously untreated EGFR-mutated (del19 or L858R). The study met its primary endpoint with a median PFS significantly longer in the amivantamab–lazertinib group than in the osimertinib group (23.7 versus 16.6 months; HR=0.70; 95% CI: 0.58-0.85; p<0.0001), with similar benefit in patients with brain metastases. Among patients with a confirmed response (336 in the amivantamab–lazertinib group and 314 in the osimertinib group), the median duration of response (DoR) was superior in the combination group, reaching 25.8 months versus 16.8 months in the osimertinib group[31]. Despite the positive results, caution should be exercised in prescribing the combination in view of the important toxicities reported. This combination strategy using amivantamab and lazertinib can be used in the second line after progression to osimertinib, as shown in the MARIPOSA 2 study. In this study, EGFR mutated patients (exon 19 deletion or L858R) were randomized to receive amivantamab-lazertinib-chemotherapy, chemotherapy, or amivantamab-chemotherapy. PFS was significantly longer for amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy versus chemotherapy, with median of 6.3 and 8.3 versus 4.2 months, respectively (HR 0.48 and 0.44, respectively; P < 0.001 for both). Objective response rate was significantly higher for amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy versus chemotherapy (64% and 63% versus 36%, respectively; P < 0.001 for both)[32]. Considering the much greater toxicity of adding lazertinib to the amivantamab and chemotherapy regimen, especially skin toxicity, paronychia, and diarrhea, with no evident benefit at this time, the combination of amivantamab and chemotherapy, without TKI, becomes interesting.

At disease progression on the first- and second-generation TKIs, it is important to perform a search for the T790M resistance mutation in exon 20 of the EGFR gene, since it is responsible for 60% of cases of acquired resistance in this scenario. The evaluation of the T790M mutation can be performed by conventional tissue biopsy, or liquid biopsy in plasma or urine, by detecting circulating tumor DNA, preferably with PCR methodology[33]. The AURA III study showed the superiority of osimertinib compared to chemotherapy in the second line after progression to first- and second-generation TKIs in patients with the T790M mutation. The median PFS was 10.1 months versus 4.4 months, favoring osimertinib (HR=0.30; 95% CI: 0.23-0.41; p<0.001). The objective response rate was also higher for osimertinib reaching 71% versus 31%[34].

Despite the great revolution in the treatment of EGFR-mutated lung cancer, patients eventually progress. Unfortunately, it has been reported that even third-generation anti-EGFRs, such as osimertinib, are being affected by new resistance mutations, such as C797S. New efforts, however, are already underway with the design of fourth-generation anti-EGFRs or even combinations of targeted therapies to overcome this new problem.[35,36]

In the adjuvant setting, targeted therapy is also indicated. All patients undergoing complete resection in stages IB–IIIA (according to the 7th AJCC edition) should undergo molecular testing for EGFR mutation. In the presence of one of the classic sensitivity mutations (del19 or L858R), adjuvant treatment with osimertinib should be considered. The data come from the ADAURA study, which randomized 682 resected patients with EGFR mutation to receive placebo or osimertinib for 3 years. The study met its primary endpoint, with 90% of patients in clinical stages II–IIIa (according to the 7th AJCC edition) being alive and disease-free at two years, compared with 44% in the placebo group (HR 0.17; 99.06% CI: 0.11–0.26; P<0.001). The study was also positive for the entire population, which included patients in EC IB[37]. In 2023, the study update showed an increase in overall survival in the population that received adjuvant osimertinib[38]. Therefore, it is the gold standard and a major advance in treatment in this setting.

Anaplastic lymphoma kinase (ALK)

ALK is a tyrosine kinase that can be aberrantly expressed in various types of tumors. In adenocarcinoma, abnormalities involve chromosomal rearrangements affecting the ALK gene locus on chromosome 2, present in approximately 3-5% of NSCLC tumors, predominantly in non-squamous histology[39]. This abnormalities results from the juxtaposition of the 5' end of the Echinoderm Microtubule-associated Protein-like 4 (EML4) gene with the 3' end of the ALK gene, forming the novel EML4-ALK fusion oncogene[40].

Given the importance and availability of specific targeted therapies, it is crucial to test for ALK alterations promptly after diagnosis, whether the disease is advanced or localized, due to the high sensitivity to ALK-targeted inhibitors. Methods can be performed on tumor samples or plasma (liquid biopsy). Available methods include NGS, FISH, and immunohistochemistry (IHC), each with its limitations[41]. In studies comparing patients with ALK-positive NSCLC assessed by FISH, IHC, or NGS (all three tests simultaneously), the positivity rates were 95% for IHC, 93% for NGS, and 82% for FISH. Concordance between IHC and NGS was 87%[42].

ALK fusion tumors are associated with a distinct clinical profile compared to other NSCLC patients, which determined unfavorable course before the advent of modern therapy: These are diagnosed at a younger age (median 51 versus 70 years), negative smoking history or <10 pack-year, predominantly adenocarcinoma histology (~97%), greater propensity for brain metastases[43].

The treatment of tumors with ALK translocations is not markedly different from other lung cancers. The use of targeted therapies has revolutionized the management and prognosis of these patients, who now experience prolonged PFS and OS, making targeted therapies the first choice whenever available[43]. The responses seen in these patients are among the best for those with actionable targets, underscoring the need for widespread and mandatory testing for all patients with non-squamous histology.

Patients with adenocarcinoma with ALK translocations show a slightly better response compared to non-mutated patients. The preferred therapy is combinations including pemetrexed. This is the treatment of choice for patients requiring urgent initiation of therapy while awaiting molecular panel results[43].

These patients generally have worse responses to immunotherapy (checkpoint inhibitors- CPI) compared to others. Additionally, there is evidence of potentially greater toxicities (hepatitis and pneumonitis) associated with immunotherapy, either concomitantly or preceding targeted therapy[44].

Targeted therapies have transformed the treatment of this malignancy, improving prognoses in previously deemed unfavorable sceneries compared to tumors without driver mutations. In metastatic patients the first-generation drug that showed superiority over chemotherapy regimens was Crizotinib. Initial studies, whether in first-line or subsequent lines, consistently showed benefits over chemotherapy. The final analysis of the PROFILE 1014 study demonstrated that at 46 months of follow-up, OS was not significantly different (HR 0.76; 95% CI: 0.55-1.05). However, after adjusting for crossover (85% of patients received crizotinib after progression), the benefit was confirmed (HR 0.35; 95% CI: 0.08-0.72)[45].

However, crizotinib has been surpassed by second-generation inhibitors, with Alectinib and Brigatinib being the most significant. Both drugs are approved by the EMA (European Medicines Agency) and FDA (Food and Drug Administration) for first-line treatment as well as after progression on crizotinib[43].

The approval of Alectinib in the first-line setting followed the ALEX study. This global study versus crizotinib demonstrated a 53% reduction in the risk of death in favor of Alectinib, with a median PFS of 35 versus 11 months (HR 0.43) and a median OS not yet reached in the Alectinib group[46,47]. Additionally, Alectinib showed significantly lower rates of overall toxicity, particularly in dermatologic and gastrointestinal areas. The PFS for brain metastases was even better, with an 84% reduction in the intervention group[48]. Similar results against crizotinib were observed in the Japanese (J-ALEX) and East Asian (ALESIA) populations, maintaining the advantage for Alectinib.[46,48]

Brigatinib is another effective option for previously untreated patients. In the ALTA-1 study, patients were randomized to receive Brigatinib or Crizotinib, with the intervention group showing benefits in PFS of 12 months, 67% versus 43% (HR 0.49; 95% CI: 0.33-0.74), with even greater benefits in the presence of baseline brain metastases. Response rates were 79% versus 26% in favor of Brigatinib. Special attention should be given to pulmonary toxicity, which was more frequent in the Brigatinib group but was mitigated with dose escalation. Other toxicities were less frequent compared to Crizotinib[49].

The third-generation ALK inhibitor is Lorlatinib, which in the CROWN study showed superiority over Crizotinib in patients with no prior treatment, specifically in stage IIIB/IV (other studies were limited to stage IV). Lorlatinib demonstrated an immature improvement in PFS, with a rate of 60% versus 8% at 60 months, and rates of 92% versus 21% in CNS, at the same time point. Unlike second-generation options, Lorlatinib had higher toxicity, particularly hypercholesterolemia and hypertriglyceridemia (>70%), and cognitive symptoms, which may impact treatment choice[50].

There are no comparative studies among these three medications, all better than crizotinib, and all medications are used continuously, and discontinued upon progression or prohibitive toxicities. Other drugs, such as Ceritinib and Ensartinib, are being tested and have shown advantages over chemotherapy or Crizotinib, but more mature results are awaited.[51,52] Due to higher response rates and benefits, patients with brain metastases are encouraged to start treatment with second- or third-generation agents.

Treatment options after progression on an ALK agent will be defined based on the first-line therapy used. A new biopsy is always encouraged due to different resistance mechanisms. As a general rule, when biopsy is not possible, patients who used Crizotinib have shown benefit, with improved PFS and OS outcomes with second-generation agents. The ALUR study compared monotherapy chemotherapy or Alectinib, showing PFS benefits with Alectinib (7.1 versus 1.6 months HR 0.32). Again, patients with CNS implants derived greater benefits[52]. Similarly, Brigatinib showed a median OS gain of 29.5 months in a phase II study after progression on Crizotinib[53].

The agent of choice after progression on a second-generation agent is Lorlatinib, as it overcomes most acquired resistance mutations and has high CNS penetration. Response rates were 73% and PFS of 11.1 months after Crizotinib, and 40% and 6.9 months after a second-generation agent, respectively. [54,55] After exhausting ALK therapies, platinum doublets are preferred, with minimal benefits from adding immunotherapy compared to non-mutated patients. The combination with anti-angiogenics is discouraged due to the increased risk of thromboembolic events[43].

Recent use has shown benefit with the second-generation agent Alectinib for 2 years compared to platinum-based chemotherapy in patients with stage IB to T3N2-IIIB per the 8th edition of the AJCC. The median disease-free survival was not reached in the Alectinib group compared to 44.4 months for the chemotherapy group (HR=0.24)[56]. The benefit was consistent across all stages. Studies with Lorlatinib and Brigatinib in the same scenario are ongoing.

c-ROS oncogene 1 (ROS-1)

ROS-1 is a receptor tyrosine kinase expressed by the homologous oncogene, c-ROS1, through its translocation with another gene, notably CD74, FIG, and SLC34A2, resulting in cellular activation and proliferation.. Its function is similar to that of the ALK gene in lung cancer (the most frequent site), but it can also be present in gastric, colorectal, and sarcomatoid lineage tumors[57].

The investigation of ROS-1 gene translocations is done within some moment other than targets, ALK and EGFR,

immediately following diagnosis, as these mutations are mutually exclusive. Although liquid biopsy evaluation is possible, the primary methods of investigation are through FISH or NGS panel testing (currently the most utilized)[58,59].

ROS-1 translocation tumors, like those with EGFR and ALK mutations, present in a distinct patient profile compared to NSCLC cases without identified driver mutations, accounting for only 1-2% of diagnosed cases. Key characteristics include, diagnosis at a younger age, negative smoking history or exposure of <10 pack-years, predominantly adenocarcinoma histology (~90%)[57].

Treatment for ROS-1 fusions is similar to other cases with driver mutations, with a preference for targeted therapy/tyrosine kinase inhibitors and reserved use of chemotherapy with or without immunotherapy for refractory cases. Unlike EGFR and ALK mutations, due to its lower incidence, studies are smaller and evidence is less robust[59].

Crizotinib, a multi-kinase inhibitor that has activity against ROS-1/MET and ALK, remains the agent of choice for first-line treatment. Evidence from Phase II studies, though limited in patient numbers, has shown favorable results, with a response rate of 72% and a median PFS of 19.2 months. The drug's adverse event profile is acceptable, though it is notable for skin and gastrointestinal toxicity, and it has poor CNS penetration. [60,61]

Other first-line medications, which are preferred when CNS involvement is present due to their better CNS penetration, include entrectinib, repotrectinib, and TRK inhibitors (ROS1/(TRK). The study leading to entrectinib's approval demonstrated a response rate of 67%, a median PFS of 15.7 months, and a 12-month OS rate of 81%, with a DoR of 15.7 months. Approximately 60% of patients had received prior therapy, especially chemotherapy. Entrectinib has a significant toxicity profile, including nausea/vomiting, edema, and cognitive impairment, necessitating close patient monitoring[62].

Repotrectinib, a more recently approved option, showed in a Phase I/II study (TRIDENT-1) that among patients who had not received TKIs, the objective response rate was 79%, with a median PFS of 36 months and an 18-month OS rate of 88%. In patients who had progressed on crizotinib, the objective response rate dropped to 35%, with a median PFS of 9 months and an OS of 25 months[58]. The toxicity profile was also significant, with over half of patients experiencing dysgeusia, dizziness, or neuropathy, and about 30% having grade 3 or higher adverse events[63].

Lorlatinib, when used as a first-line treatment, also yielded relevant data with a response rate of 62%, a PFS of 21 months, and a DoR of 25.3 months, along with better CNS penetration. Its adverse event profile is similar to that of patients with ALK mutations[64].

Upon progression on an ALK agent, biopsy is recommended whenever possible. For a new line of treatment, a switch to another later-generation ROS-1 agent is preferred. Repotrectinib demonstrated an objective response rate of 38%, with a median DoR of 14.8 months and a PFS of 9 months in this context[58]. Cabozantinib also showed efficacy in a similar context[65]. When resistance to multiple ALK agents occurs, treatment typically involves cytotoxic chemotherapy. Like ALK-positive tumors, ROS1-positive tumors appear to have greater sensitivity to pemetrexed-based chemotherapy[66], and caution is advised with anti-angiogenic agents due to the risk of thromboembolic events[67].

Kirsten rat sarcoma viral oncogene homolog (KRAS)

Activating mutations in KRAS are present in 25–39% of non-squamous NSCLCs and are associated with smoking[68]. The KRAS G12C variant is the most frequent, occurring in 13–16% of lung adenocarcinomas[69]. Although long considered undruggable, KRAS has evolved from a prognostic to a predictive biomarker since the approval of sotorasib in 2021[70].

CodeBreaK 200 was a phase 3 study comparing KRAS G12C inhibitor, sotorasib, to standard-of-care docetaxel in patients with previously treated advanced KRAS G12C-mutant NSCLC. Sotorasib was statistically superior to docetaxel, with median PFS of 5.6 months compared with 4.5 months (HR:0.66), and showed a better safety profile[71].

Adagrasib received FDA approval based on phase I-II KRYSTAL-01 trial, also in the second-line setting. The primary endpoint of this trial was objective response, with 42.9%. The median PFS was 6.5 months, and the OS was 12.6 months[72].

To improve outcomes and survival, newer and more potent KRAS G12C inhibitors are in development. Divasasib, for example, was evaluated in solid tumors, showing an ORR of 53.4% and median PFS of 13,1 months in the NSCLC cohort in the second and third line settings[73].

Additionally, combinations of these drugs with immune-checkpoint inhibitors or chemotherapy have been evaluated in NSCLC patients, although larger confirmatory studies are needed. The combination of sotorasib and chemotherapy seems particularly promising for patients with poor prognosis co-mutations such as KEAP-1 and STK-11[74-77].

v-Raf murine sarcoma viral oncogene homolog B (BRAF)

BRAF mutations have been reported in 3% to 5% of NSCLC cases[11], with the BRAF V600E mutation present in 50% of these. Based on phase I and II trials, most guidelines recommend the use of BRAF and MEK inhibitors for metastatic patients harboring the BRAF V600E mutation, both as first-line or subsequent treatment. [78,79]

The indication of dabrafenib and trametinib is supported by a phase II trial that included 57 pretreated and 36 treatment-naive NSCLC patients harboring BRAF V600E mutation. The ORR were 68.4% and 63.9%, respectively. At the 5-year follow-up, the median PFS was 10.8 months, and the median OS was 17 months in the first-line cohort, with similar responses observed in the pretreated cohort[80].

The BRAF inhibitor encorafenib, in combination with the MEK inhibitor binimetinib, was also evaluated in a phase

II trial for the same scenario and patient population with the V600E mutation. The ORR was 75% in treatment-naïve patients and 46% in previously treated patients. The median PFS was not estimable for treatment-naive patients and was 9.3 months for those who were previously treated[81].

Rearranged during transfection (RET)

RET fusions or rearrangements have been identified in 1.0%–2.0% of NSCLC patients[82]. These genetic changes are associated with younger age, non-smoking history, a high rate of brain metastases at diagnosis, and an immunologically 'cold' tumor microenvironment.[83,84]

The best activity was demonstrated with specific RET TKIs, such as selpercatinib and pralsetinib, both approved by the FDA. The phase III LIBRETTO-431 trial randomized untreated RET fusion–positive NSCLC patients to receive selpercatinib or platinum-based chemotherapy with or without pembrolizumab. The median PFS was 24.8 months for RET-TKI compared to 11.2 months in the control arm, with an ORR of 84% for selpercatinib. The intracranial activity of selpercatinib was confirmed, with central nervous system response observed in 82% of patients with brain metastases at baseline. Overall survival data remain immature[85].

In the phase I and II ARROW trial, pralsetinib resulted in a response rate of 61% in patients who had received previous platinum chemotherapy and 70% in treatment-naive patients who were not candidates for standard therapies, with 11% achieving a complete response. The median PFS was 17.1 months[86].

Mesenchymal-to-epithelial transition (MET)

Oncogenic alterations in MET receptor include METex14 skipping mutations, MET gene copy number gain or amplification, and MET protein overexpression[87]. Approximately 2% to 4% of advanced NSCLC cases harbor METex14 skipping mutations, the best-defined predictive biomarker for the use of MET tyrosine kinase inhibitors. These patients tend to be older and are importantly related to sarcomatoid-histology NSCLC (approximately 20%)[88,89].

Capmatinib and tepotinib are highly selective oral MET inhibitors indicated to advanced NSCLC with METex14 skipping mutations, based on phase II trials. The phase II VISION trial demonstrated good clinical outcomes with tepotinib, with an ORR of 46% and a median PFS of 8.5 months in pretreated patients[90]. The long-term follow up of the VISION trial showed an ORR of 57.3% and a median DoR of 46.4 months in treatment-naive patients[91].

In the GEOMETRY mono-1 phase II trial with capmatinib, the response rate was 41% in pretreated patients and 68% in treatment-naive patients, with PFS of 9.7 months and 12.6 months, respectively[92].

Savolitinib, a selective MET tyrosine-kinase inhibitor, has also shown activity in this NSCLC subgroup, with ongoing trials[93].

Human epidermal growth factor receptor 2 (HER-2)

Approximately 2%-4% of NSCLC are driven by HER2 mutations. This mutation is associated with female sex, never-smoking history, a poor prognosis, and a higher incidence of brain metastases. [94,95]

The Destiny Lung 02 trial was a phase II study that included patients with advanced NSCLC harboring HER2 mutations who had received at least one previous treatment (platinum-based chemotherapy) in the advanced setting. The final analysis showed an ORR of 50%, a median PFS of 10 months and a median OS of 19 months with a dose of 5.4 mg/kg. Pneumonitis was reported in 14.9% of patients, but most events were grade 1 or 2[96,97].

Neurotrophic receptor tyrosine kinase (NTRK)

NTRK gene fusions involving *NTRK1*, *NTRK2*, or *NTRK3* are very infrequent oncogenic drivers, found in around 0.2% of NSCLC[98].

Both larotrectinib, a specific TRK inhibitor, and entrectinib, a multikinase TRK inhibitor, have gained tumor-agnostic FDA approval for patients with tumors harboring NTRK rearrangements. Larotrectinib was evaluated in a cohort of 30 pretreated NSCLC patients with NTRK rearrangement, demonstrating an ORR of 74%, a median DoR of 33.9 months, and a PFS of 33.0 months[99].

Entrectinib is also active in TRK fusion lung cancers and was designed to have high CNS penetration. An integrated analysis of three phase I/II trials (ALKA-372-001, STARTRK-1, STARTRK-2) evaluated 31 NSCLC patients harboring NTRK rearrangements, showing an ORR of 64.5% and an intracranial ORR of 60%. The median DoR was 27.1 months, and the median PFS was 20.8 months[100].

Discussion

In the early 1900s, Nobel laureate Paul Ehrlich postulated a therapy that would be ideal for specifically combating a disease. A drug that would precisely target an invader, which, if bound to a toxic chemical, would act like a missile, delivering a destructive payload directly to the disease. Ehrlich called the drug the "Magische Kugel"; what we know as "Magic Bullet," or better defined in today's terms, as molecularly targeted therapy. Such a weapon could be used to fight cancer. A century has passed since then, and today science has provided us not only with the destructive payload, but also the missile[101].

In modern oncology, one of the main targets studied are tyrosine kinases receptors, which are a subclass of transmembrane growth factor receptors. They regulate several functions in normal cells, in addition to playing a crucial role in oncogenesis. Therefore, great efforts have been made to understand their role in the most diverse cellular processes, such as proliferation, migration, differentiation and survival. When mutated, structurally altered or constitutively activated, TKRs become potent oncoproteins, leading to tumor development and progression. In view of this, TKRs and their ligands have become excellent therapeutic targets through their inhibition, either by antibodies or by small molecules, are known as tyrosine kinase inhibitors (TKIs)[102]. These currently recognizable oncoproteins can be rapidly identified and form the basis of an improved understanding of the physiopathology of many lung cancers. The current technology allows us to get early

genomic information from tumor tissue with the capability of offering patients molecularly targeted inhibitors with dramatic effect on disease behavior, performing as predictive factors for therapeutic and prognostic results.

Lung cancer has become a prototype of an oncological disease in which targeted therapy can transform a potentially serious and fatal condition into a chronic disease. Consequently, it is one of the greatest success stories in the history of modern oncology. In view of this, molecular characterization of tumor tissue, especially in the case of adenocarcinomas, is currently essential in defining the treatment strategy for advanced disease and has increasingly become a standard of care in the early stages, following recent evidence of a benefit with the use of targeted agents in the adjuvant setting[37].

Since the demonstration of increased survival in patients with lung adenocarcinoma treated with platinum-based therapy, which is of limited benefit, we are now facing a momentum where a different class of non curative therapy is available. There is benefit in symptom relief, rate of regression and responses, prolongation of survival of treated patients at a usually low toxicity profile. Again we need to abandon any nihilistic approach that might still exist in reference to metastatic lung adenocarcinoma. A disease that can be effectively treated once the drivers are identified.

Obviously, there are problems related to the use of targeted therapy, such as treatment resistance. In addition, the abundance of proliferation pathways and cross talk between different signals induce continuous tumor growth, directly affecting the inhibitory effects of molecular targeted therapy[103]. To combat these mechanisms, lung cancer treatment continues to evolve, with the development of later-generation TKIs or combination therapies, for example[35,36]. Still in the clinical setting, other limitations include accessibility and costs related to treatment, in addition to the tools necessary for diagnosis involving an adequate tumor biopsy with sufficient material for a broad molecular analysis[104]. Insufficient material sometimes subjects the patient to new procedures such as bronchoscopy and image-guided biopsies, increasing morbidity.

As a prototype of targeted therapy, new developments emerge every year. At the 2024 American Congress of Oncology (ASCO), lung cancer was the highlight. The LAURA study brought us news with the use of osimertinib after definitive treatment with chemotherapy plus radiotherapy in patients with EGFR mutation and unresectable EC III lung cancer[105]. Antibody-drug conjugates (ADCs) have also been gaining ground. The Luminosity study brought us Telisotuzumab Vedotin in patients with c-MET overexpression, bringing interesting response rates in polytreated patients[106].

It is worth emphasizing that both academic and pharmaceutical research should remain focused on evaluating molecular targets for the treatment of lung cancer and others. These targets, actionable ones, are mostly restricted to adenocarcinomas of lung but the markers of an “immune tumor” can be recognized and are another door for effective therapies with checkpoints inhibitors. Future research should also focus on unraveling the mechanisms of acquired resistance, defining the ideal therapeutic sequence, and exploring combination treatments in order to achieve rapid and complete eradication of tumor cells.

A prevalent disease, NSCLC, most frequently adenocarcinomas, in way over 50% of the cases have actionable mutation or genetic fusion in non selected populations. These features should be identified early on in the diagnostic process in order to offer this large number of patients the precise drug that has proven superior to our standard of care from the late part of last century.

Conclusion

This review summarized clinical data regarding the use of targeted therapy in patients with localized and metastatic lung adenocarcinoma, focusing on classical therapies and new pharmacological advances.

The treatment of lung adenocarcinoma has changed radically since the role of targeted mutations in the carcinogenesis of this disease became better understood. The Lung Cancer Mutation Consortium showed that approximately 64% of patients with lung adenocarcinoma have some oncogenic driver[107], although the biological significance is not always understood. The idea of a genetic signature that can be treated with targeted therapy has motivated preclinical and clinical studies in the search for drugs to target the mutations found, in addition to improving existing treatments. We should encourage the inclusion of these patients in clinical trials whenever possible, and currently, all patients with advanced lung adenocarcinoma should undergo a broad panel for molecular evaluation before starting treatment.

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