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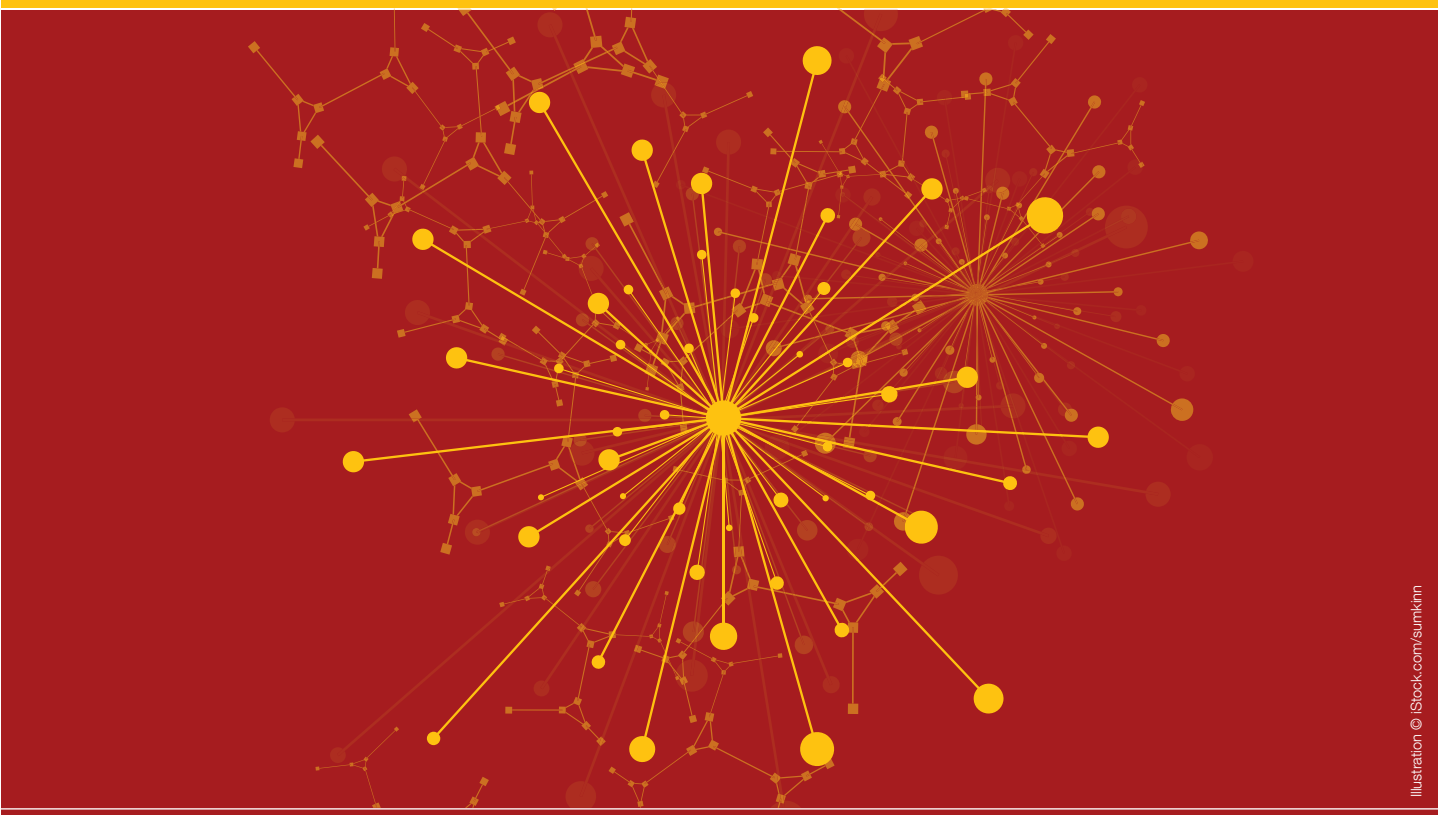

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GLOBAL PERSPECTIVE ON LUNG CANCER: DISEASE MANAGEMENT IN BRAZIL & LUNG CANCER RESEARCH IN ASIA

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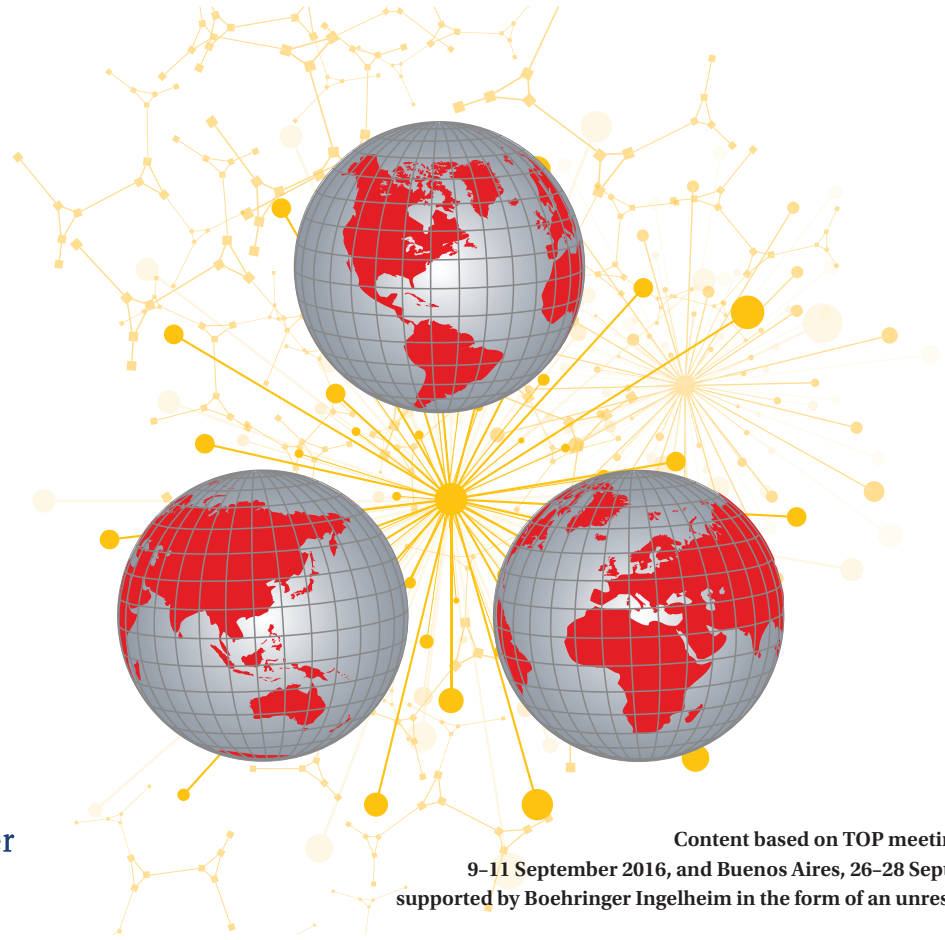

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Global perspective on lung cancer: disease management in Brazil & lung cancer research in Asia

A challenge for less developed nations

Cancer incidence rates have increased in most countries since 1990 [1]. "This trend is a particular threat to developing nations with health systems that are ill-equipped to deal with complex and expensive cancer treatments," emphasized Carlos H. Barrios, MD, Hospital do Câncer Mãe de Deus, PUCRS School of Medicine, Porto Alegre, Brazil. Overall, 56 % of new cancer cases and 62 % of cancer-related deaths occur in developing countries.

Lung cancer is the most common cancer in men worldwide and the leading cause of cancer death in men in 87 countries and in women in 26 countries. Global patterns of mortality mirror those of incidence, because survival varies little by region. As Dr. Barrios explained, 58 % of lung cancer cases occur in less developed regions **(Table 1)** [2]. According to the Brazilian National Cancer Institute, 27,000 lung cancer cases were diagnosed in Brazil in 2014, constituting 9.4 % of total incident cancer cases [3]. Lung cancer is the second and fourth most common type of cancer among men and women, respectively **(Table 2)**. The age-standardized 5-year survival in Brazilian lung cancer patients amounts to 18 % (worldwide: 10 %–20 %) [4]. "Lung cancer is the main cause of cancer death in Brazil," Dr. Barrios stated.

Nevertheless, data on diagnosis, staging, treatment and outcomes are generally scarce, and the lengthy clinical research approval process limits access to clinical trial opportunities. The entire Latin American region is characterized by significant inequities between public and private health systems with regard to access to diagnosis, therapy and molecular testing.

Risk factors: smoking and pollution

Of course, smoking accounts for the majority of lung cancer cases. The total prevalence of adult tobacco use in Brazil currently amounts to 17 %, with men and women making up 22 % and 13 %, respectively [5]. However, tobacco use is considerably more common in young people aged 13 to 15 (30.1 %); here, the female smoking rate (30.8 %) even exceeds the male smoking rate (28.7 %). For 2020, the population-attributable fractions of lung cancer burden associated with smoking in Brazil were calculated at 83.28 % and 64.78 % for men and women, respectively [6].

TABLE 1
Global distribution of lung cancer cases (percentages of 180,000,000 cases)

Region	%
China	35.8
India	3.9
Other East and Central Asian countries	15.6
Europe	22.5
Northern America	13.1
Latin America & the Caribbean	4.6
Middle East & North Africa	2.9
Sub-Saharan Africa	0.9
Oceania	0.8

This illustrates the necessity of national anti-tobacco policies that have been successfully implemented in Brazil in the past. No-smoking rules in all public spaces, higher cigarette prices, and health warning labels on cigarette packages have contributed to decreasing tobacco use. "Smoking prevalence has diminished by around 50 %, as have tobacco-related deaths," Dr. Barrios emphasized. In 2008, 18.9 % of men and 11.5 % of women aged ≥ 15 years smoked on a daily basis; this represents a considerable improvement compared to the rates assessed in 1989 (43.3 % and 27 %, respectively).

Another risk factor of growing importance is ambient air pollution, which is promoted by economic growth and increased urbanization [7]. As Dr. Barrios pointed out, epidemiological evidence that links air pollution to mortality from lung cancer is robust. High-quality scientific research that addresses these risks and the ability of local health authorities to understand and respond to them are required to solve the conflict between economic development and the preservation of human health. "However, this is currently far from being achieved," Dr. Barrios said.

Evidence on the usefulness of screening

Screening of lung cancer as a population-based strategy was assessed in the Brazilian Lung Cancer Screening Trial (BRELT1) [8], which followed the same criteria as the US National Lung Screen-

TABLE 2
Brazilian National Cancer Institute estimates for new cancer cases in 2016 in men and women

Men	n	%
	61,200	28.6%
Lung	**17,330**	**8.1%**
Colon & rectum	16,660	7.8%
Stomach	12,920	6.0%
Oral cavity	11,140	5.2%
Esophagus	7,950	3.7%
Urinary bladder	7,200	3.4%
Larynx	6,360	3.0%
Leukemias	5,540	2.6%
CNS	5,440	2.5%
Women	**n**	**%**
Breast	57,960	28.1%
Colon & rectum	17,620	8.6%
Uterine cervix	16,340	7.9%
Lung	**10,890**	**5.3%**
Stomach	7,600	3.7%
Uterine corpus	6,950	3.4%
Ovary	6,150	3.0%
Thyroid	5,870	2.9%
NHL	5,030	2.4%
CNS	4,830	2.3%

ing Trial (NLST) [9]. From January 2013 to July 2014, 790 people participated in the program. "The positive scan rate was 39.4, and NSCLC was diagnosed in 10 cases, which equals 1.3 %," Dr. Barrios reported. "Most of these patients belonged to stage I." In the NLST, the detection rate was 1.98 %. No routine population-based program has been implemented in Brazil based on this experience, however.

General screening might make sense, though, because early-stage presentation is a relatively infrequent event in Brazilian lung cancer patients. According to an analysis conducted between 2000 and 2010 in 20,850 lung cancer patients, only 8.8 % had stage I disease [10]. This compared unfavourably to the rates assessed in the United States (15.4 %; 2004-2010) and the United Kingdom (14.5 %; 2003–2006).

Diagnosis in Brazil: imaging

With regard to diagnostic procedures, inequalities between the lower-income and the higher-income segments of the Brazilian population are striking. A survey conducted in 2005 showed that the rate of CT scans available per 1,000,000 inhabitants was 4.9 in the public health system and 30.8 in the private health system [10, 11]. "The rates in the private sector resemble those in developed countries," noted Dr. Barrios (31.5 in the United States and 32.2 in Japan). Also, there are disparities according to the geographic distribution, with lower CT availability in the northern and northeastern regions of Brazil, which are less wealthy than the regions in the South.

The use of PET scans for lung cancer was approved in 2010, but this technology has not been implemented until 2014 by Brazil's publicly funded health care system. Over the last years, the number of PET scan facilities has increased markedly. As Dr. Barrios said, 124 PET scanners and 15 cyclotrons were distributed throughout 21 of the 27 states in 2014. "However, the lower availability in the public health system is again striking."

With respect to bronchoscopy, the SBPT survey showed that 56.7 % of respondents performed at least 100 bronchoscopies per year, which meets international recommendations [10, 12]. For bronchoscopy-guided transbronchial needle aspiration, satisfactory samples were obtained in 57 %, and definitive diagnosis was made in 81 %. Endobronchial ultrasound has been introduced only recently at large centers. According to early experiences, 74 % of examinations yielded adequate specimens.

Molecular testing

"The introduction of molecular testing is key to improving therapeutic results in patients with lung cancer," Dr. Barrios pointed out. As an analysis of the Lung Cancer Mutation Consortium showed, lung cancer patients with oncogenic driver mutations who received genotype-directed therapy had significantly longer median overall survival than those who were not treated with genotype-directed therapy (3.5 vs. 2.4 years; HR, 0.69; p = 0.006) [13]. From a global perspective, however, it must be said that access, affordability and incorporation strategies remain significant challenges, particularly in low-income and middle-income countries. Issues in the context of the incorporation of molecular testing into clinical routine include factors such as reimbursement, access to targeted therapies, and patient education **(Table 3)**.

Among molecularly targeted therapies, erlotinib, gefitinib, afatinib, and crizotinib are available for the treatment of lung cancer in Brazil. However, a marketing survey conducted in 1,700 patients in 2014 revealed that fewer than 50 % are tested for their *EGFR* mutation status in Brazil [10]. "It was estimated that 60 % of cases are tested in the private sector, while this proportion was 30 % or less in the public setting," Dr. Barrios said. "The respective percentages are likely to be considerably lower for *EML4-ALK* rearrangement testing." In Brazilian study cohorts, the prevalence of *EGFR* mutations ranged between 22 % and 33 % [10]. The frequency of *EML4-ALK* translocations has been estimated at 3 %–4 %.

Treatment: surgery and radiotherapy

Approximately 25 % of Brazilian lung cancer patients overall and 61 % of those with stage I disease undergo surgery [10, 14–16]. Patients with lower educational levels are less likely to receive surgery. This might also be due to geographic inequalities: overall, 763 thoracic surgeons work in Brazil, but 51 % of them practice in cities with more than 1 million inhabitants.

Shortages are also a significant issue in the context of radiotherapy, as a deficiency in machines prevents full treatment coverage in the country. "Due to the lack of 150 radiotherapy machines, the treatment demands of approximately 100,000 patients per year cannot be met," Dr. Barrios stressed [10, 17, 18]. The average waiting time is 113 days, which mainly applies to public centers. As for surgeons, the distribution of radiologists is uneven across the country, because most of the 550 radiation oncologists work in the Southeast region. Only few centers offer stereotactic body radiotherapy or stereotactic ablative radiotherapy for the treatment of localized disease.

Belated and limited access to systemic agents

Significant delays in the approval of drugs by local regulatory agencies tend to impede systemic oncological treatment in Brazil. For example, the ALK inhibitor crizotinib was registered in 2016, while approval by the FDA occurred five years earlier, in 2011. It has been calculated that 772 patients died in Brazil owing to the lack of access to crizotinib [19]. Access to systemic therapy is generally inadequate. Pemetrexed is still unavailable in the public health system, and bevacizumab can only be obtained by patients with private health coverage. "EGFR TKIs were included in the public

TABLE 3
Issues with regard to the incorporation of molecular testing into clinical routine

+ Reimbursement and logistics
+ Access to targeted therapies
+ Patient education and medical information
+ Established laboratory infrastructure for molecular testing (limited to a few large centers/cities)

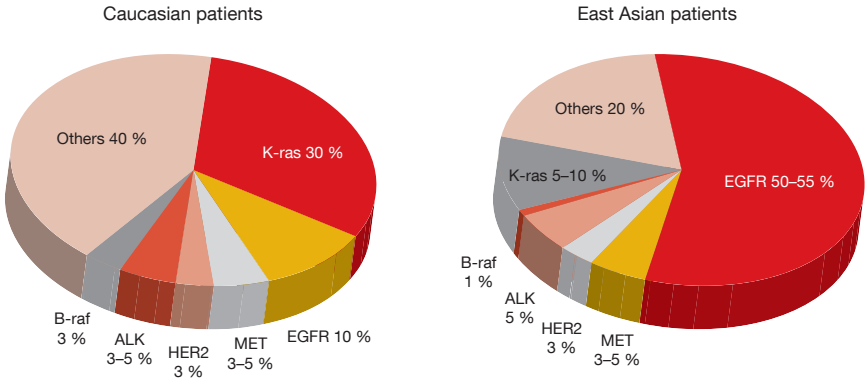


Figure 1: Differences in distribution of oncogenic driver mutations between Caucasian patients and East Asian patients

health system in 2015, but both mutation testing and drugs are neither adequately covered nor routinely provided to patients," Dr. Barrios reported.

The expert listed several major barriers to access to high-cost drugs in the Latin American region, such as the fact that each government has different policies for drug approval and the lack of adequate investments in research and development [20]. Limitations in current lung cancer services are not necessarily considered a priority. Also, affordability of the new targeted medications poses problems; policies are called for to allow better coverage with the most important drugs.

Measures to be taken include reinforcement of the role of tobacco control and stimulation of programs directed at the whole population and particularly teenagers. Furthermore, collection of high-quality epidemiological and health-economy data is necessary. "We should stimulate productive dialogue between medical societies, advocacy groups, government, pharmaceutical companies, and regulatory agencies," Dr. Barrios suggested. Local funding should be dedicated to lung cancer prevention, diagnosis and treatment research. Development of research units, participation in clinical trials and international collaboration need to be stimulated.

Lung cancer research in Asia: patients with distinct genomics

With a total population of 4.227 million, Asia is the most densely populated continent. This also means that it has the largest percentage of lung cancer patients in the world, which provides ample opportunity to study this disease. Asia as a place to recruit patients and conduct clinical trials has gained importance after the detection of genetic driver alterations such as *EGFR* mutations that commenced in 2004. "A unique feature of lung cancer patients in East Asia is that driver alterations differ from those in western populations", explained Chia-Chi Lin, MD, PhD, Department of Oncology, National Taiwan University Hospital, and Graduate Institute of Oncology, National Taiwan University College of Medicine **(Figure 1)**.

In East Asia, *EGFR* mutation is present in approximately 50 % of NSCLC patients, as opposed to only 10% in the western population. This means that patient enrichment in clinical trials can be achieved rather effortlessly. Other molecular alterations such as *MET*, *HER2* and *ALK* aberrations show similar prevalence across the ethnicities, while the proportion of *KRAS*-positive tumors is markedly smaller in East Asian patients than in Caucasian patients. Important achievements that were mainly promoted at Asian sites included the establishment of EGFR-targeted tyrosine kinase inhibitors (EGFR TKIs) in patients with *EGFR*-mutation-positive NSCLC and the identification of the EML4-ALK, ROS1 and RET fusion proteins as targetable drivers of genetic alteration.

Large phase III trials of Asian origin

Not surprisingly, the Asian contribution to the advancement of NSCLC treatment in the *EGFR*-targeted area has been huge. "The important phase III trials to establish the efficacy of EGFR TKIs as first-line treatment were conducted in Asia," Dr. Lin reported. These comprise NEJ002 (gefitinib vs. carboplatin and paclitaxel) [21], WJTOG3405 (gefitinib vs. cisplatin and docetaxel) [22], IPASS (gefitinib vs. carboplatin and paclitaxel) [23], OPTIMAL (erlotinib vs. carboplatin and gemcitabine) [24], and LUX-Lung 6 (afatinib vs. cisplatin and gemcitabine) [25]. "All of them enrolled cohorts with patient numbers ranging from more than 100 to more than 1,000." Likewise, the large phase III LUX-Lung 3 trial that compared afatinib with cisplatin plus pemetrexed contained mainly East Asian patients, even though it was conducted globally [26].

The combined analysis of the data from LUX-Lung 3 and 6 led to further classification of lung cancer [27]. "*EGFR* mutations were divided into deletion 19 and L858R mutations, which responded differently to treatment," Dr. Lin emphasized. Patients with deletion 19 derived a significant overall survival benefit of 11 months from afatinib therapy, while those with L858R mutation fared better with chemotherapy than with afatinib.

Two aspects within the *EGFR*-mutant lung cancer research landscape are currently investigated at Asian sites. They relate to overcoming T790M resistance mutation on one hand and to the study of special populations on the other. Specific drugs have been developed with the aim of overcoming T790M resistance mutation. "The phase I development for almost all of these agents has been conducted in Asia," Dr. Lin pointed out. For instance, development of the third-generation EGFR TKI osimertinib, which is the first drug of this type to gain approval, took place in Asia from the very beginning.

CNS-targeted agents on the rise

The topic of special populations has become clinically relevant in light of the major improvements in life expectancy that have been achieved with modern agents. Many patients with *EGFR*-mutant adenocarcinoma who receive optimal treatment will live for time spans unprecedented in this setting. "In the past, we rarely ever saw any NSCLC patients developing detrimental conse-

quences such as brain metastases or leptomeningeal disease," Dr. Lin noted. "Now this is very common." Combined data from the LUX-Lung 3 and 6 trials indicated that patients with brain metastases and common *EGFR* mutations also derive benefit from afatinib treatment **(Figure 2)** [28].

Updated findings from the phase I BLOOM study demonstrated intracranial activity of osimertinib in heavily pre-treated patients with leptomeningeal disease due to *EGFR*-mutant NSCLC [29]. Apart from targeting T790M as well as activating *EGFR* mutations, osimertinib crosses the blood-brain barrier to a greater extent than other EGFR TKIs. This is also true for AZD3759, which is the first EGFR inhibitor designed to tackle central nervous system metastases in patients with *EGFR*-positive NSCLC. According to a phase I trial, AZD3759, at doses of ≥50 twice daily, induced intracranial tumor shrinkage in 11 of 21 patients with brain metastases [30]. Phase II studies have been initiated. "Thanks to this type of treatment, patients can be spared whole-brain radiation therapy that has late sequelae such as cognitive dysfunction," Dr. Lin stressed.

Outlook: immunotherapy in patients with driver mutations

The first drug to be approved for the treatment of NSCLC patients with *EML4-ALK* rearrangement was crizotinib. Almost half of the patients participating in the two pivotal phase III trials PROFILE 1014 and 1007 that compared crizotinib with first-line and second-line chemotherapy, respectively, were Asian [31, 32]. As crizotinib-treated patients invariably develop resistance over time, this treatment is usually succeeded by second-generation ALK inhibitors such as ceritinib. "The ASCEND-1 and ASCEND-2 studies that investigated ceritinib were conducted in Asia," Dr. Lin said [33, 34]. Asian sites are also playing a prominent role in the evaluation of the second-generation ALK inhibitors alectinib and brigatinib.

Referring to future aspects of lung cancer research in Asia, Dr. Lin noted that immunotherapy is of course a major issue in the months and years to come. "I believe that Asian centers can play a very important role in determining the role of immunotherapy in lung cancer, especially in the presence of genetic driver alterations," the expert said. One obvious question relates to the ideal combinations of immunotherapy and targeted therapies for patients with driver mutations. As Dr. Lin pointed out, the agents can be used concurrently or sequentially. "However, preliminary results showed that combinations might not be the best option because of common toxicities." A viable concept might therefore be determination of the sequence with which to achieve the greatest benefit for the patient. "In the future, we will use our infrastructure and the present energy as a momentum to continue further in the field of lung cancer research," Dr. Lin concluded. ■

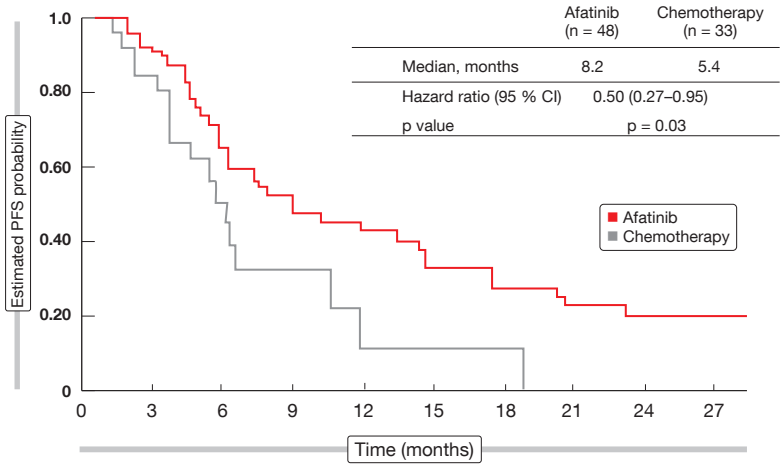
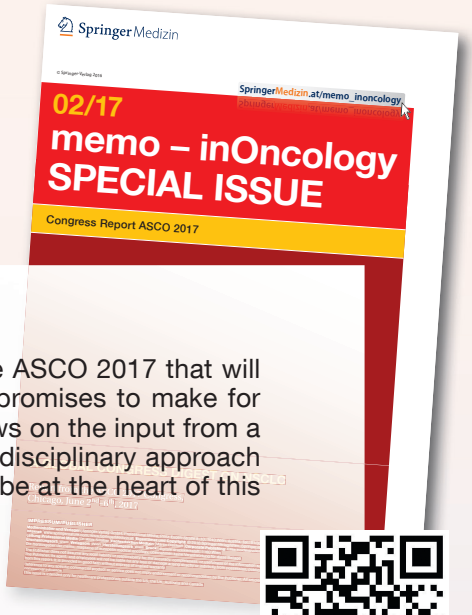


Figure 2: Progression-free survival benefit obtained with afatinib vs. chemotherapy in patients with brain metastases and common *EGFR* mutations (combined analysis from LUX-Lung 3 and 6)

REFERENCES

1 Global Burden of Disease Cancer Collaboration, The global burden of cancer 2013. JAMA Oncol 2015; 1(4): 505-527
2 Cancer.org/CancerAtlas, American Cancer Society, Inc.
3 http/inca.gov.br. Accessed on 01/02/16
4 Souza MC et al., Trends in lung cancer mortality in Brazil from the 1980s into the early 21st century: age-period-cohort analysis. Cad Saude Publica 2012; 28: 21-30
5 www.thelancet.com/commissions/planning-cancer-control-in-latin-america-and-the-Caribbean
6 Azevedo ESG et al., The fraction of cancer attributable to ways of life, infections, occupation, and environmental agents in Brazil in 2020. PLoS One 2016; 11: e0148761
7 https://air.plumelabs.com/en/year/sao-paulo
8 dos Santos RS et al., Do current lung cancer screening guidelines apply for populations with high prevalence of granulomatous disease? Results from the First Brazilian Lung Cancer Screening Trial (BRELT1). Ann Thorac Surg 2016; 101: 481-488
9 National Lung Screening Trial Research Team, Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011; 365(5): 395-409
10 Araujo LH et al., Lung Cancer in Brazil. Submitted
11 http://www.ibge.gov.br
12 Tedde ML et al., Endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis and staging of mediastinal lymphadenopathy: initial experience in Brazil. J Bras Pneumol 2012; 38: 33-40
13 Kris MG et al., Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. JAMA 2014; 311: 1998-2006
14 Sánchez PG et al., Lobectomy for treating bronchial carcinoma: analysis of comorbidities and their impact on postoperative morbidity and mortality. J Bras Pneumol 2006; 32: 495-504
15 Stanzani F et al., Morbidity, mortality, and categorization of the risk of perioperative complications in lung cancer patients. J Bras Pneumol 2014; 40: 21-29
16 http://fosp.saude.sp.gov.br
17 Moraes FY et al., Brazil's challenges and opportunities. Int J Radiat Oncol Biol Phys 2015; 92: 707-712
18 http://cnen.gov.br
19 Barrios PM et al., Impact of regulatory delays in approving oncology drugs in a developing country: mortality associated with lack of access to crizotinib in Brazil. WCLC 2016, ORAL 27.07
20 Raez LE et al., Clin Lung Cancer 2016 (in press)
21 Maemondo M et al., Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010; 362: 2380-2388
22 Mitsudomi T et al., Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010; 11: 121-128
23 Mok TS et al., Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009; 361: 947-957
24 Zhou C et al., Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011; 12: 735-742
25 Wu YL et al., Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol 2014; 15: 213-222
26 Sequist LV et al., Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013; 31: 3327-3334
27 Yang JC-H et al., Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol 2015; 16: 141-151
28 Schuler M et al., First-line afatinib versus chemotherapy in patients with non-small cell lung cancer and common epidermal growth factor receptor gene mutations and brain metastases. J Thorac Oncol 2016; 11(3): 380-390
29 Yang J C-H et al., Osimertinib activity in patients (pts) with leptomeningeal (LM) disease from non-small cell lung cancer (NSCLC): Updated results from BLOOM, a phase I study. J Clin Oncol 34, 2016 (suppl; abstr 9002)
30 Ahn MJ et al., Phase I study of AZD3759, a CNS penetrable EGFR inhibitor, for the treatment of non-small-cell lung cancer (NSCLC) with brain metastasis (BM) and leptomeningeal metastasis (LM). J Clin Oncol 34, 2016 (suppl; abstr 9003)
31 Solomon BJ et al., First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 2014; 371: 2167-2177
32 Shaw AT et al., Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013; 368: 2385-2394
33 Kim DW et al., Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. Lancet Oncol 2016; 17: 452-463
34 Mok T et al., ASCEND-2: A single-arm, open-label, multicenter phase II study of ceritinib in adult patients (pts) with ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC) previously treated with chemotherapy and crizotinib (CRZ). J Clin Oncol 33, 2015 (suppl; abstr 8059)



Forthcoming Special Issue

This special issue will be offering a synopsis from the ASCO 2017 that will be held in Chicago, in June of this year. The report promises to make for stimulating reading, as the ASCO Congress itself draws on the input from a number of partner organizations, representing a multidisciplinary approach to cancer treatment and care. Again, lung cancer will be at the heart of this special issue.

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