Lung cancers represent a more large landscape than well-known histological categories including lung adenocarcinoma (45% of cases), squamous cell carcinoma (25%), large cell carcinoma (10%) and small cell lung carcinoma (20%). Since 2004, when epidermal growth factor receptor (EGFR) mutations were discovered to give sensitivity to tyrosine kinase inhibitors (TKIs) in lung adenocar cinomas, developments had showed that lung cancer are molecularly distinct with different therapeutic vulnerabilities (1).

Increasingly molecular profiles are detected to determine the best treatment option for each lung cancer patient. Actually, there is large scenery of rarer drug gable gene mutations among non-small-cell lung cancer (NSCLC) subgroups. Targeted therapy is now a standard of care for patients with a NSCLC harbouring EGFR mutations, and anaplastic lymphoma kinase (ALK) rearrangements (2). In addition to ALK-rearrangements, other gene fusions had been discovered involving the tyrosine kinases ROS1 and RET. RET alterations are found in about 1–2% of unselected lung adenocarcinomas patients, reaching a frequency of about 6% among never-smokers patients, with tumors not-harbouring other known driver mutations (9-11).

While the functional consequences and the clinical relevance of RET fusions in lung adenocarcinoma are not fully understood, they are oncogenic in vitro and in vivo. Ju and colleagues reported for the first time a case of RET fusion in lung cancer in 2011 (12). Since then several groups found RET fusions, detecting a new molecular subset of NSCLC. Wang et al. examined 936 Chinese patients with surgically resected NSCLC to study the distribution of mutations among NSCLC, including RET fusion gene (13). This was found only in 13 patients, with tumors not-harbouring other known driver mutations (9-11).
never-smokers status, smaller primary lesion, early lymph node metastases, poor differentiation, a solid-predominant subtype, and a shorter relapse-free survival.

Because the growth of these tumors is strongly depending on RET activity, suppression of RET could be a potent therapeutic treatment. TKIs commonly used in clinical practice, as vandetanib, sunitinib or sorafenib, in in vitro models target RET kinase activity, suggesting that patients with NSCLC harbouring a RET alteration could be treatable with a TKI (9,11). There are limited retrospective and prospective data correlating the presence of RET fusions and the response to any particular therapy.

A clinical trial currently ongoing in RET fusion positive NSCLC shows preliminary data suggesting that these tumors may also be responsive to cabozantinib, a TKI with multiple targets including also vascular endothelial growth factor (VEGF) receptor 2, that can inhibit RET (NCT01639508) (14). Among a total of 31 patients with pan-negative lung adenocarcinoma, RET fusions were found in five patients. Three of them were eligible for treatment with cabozantinib, reporting two cases of partial response (PR) and one case of stable disease (SD).

However, given that RET fusions are uncommon genomic alterations, prospective trials may be difficult to implement.

In this context, data from the Global Multicenter RET Registry (GLORY) could be very useful, especially considering that clinicians tend to investigate uncommon genomic alterations to treat patients with tumors harbouring these driver mutations (15).

The aim of the study of Gatsuchi et al. colleagues was to illustrate the clinicopathologic characteristics of patients with advanced RET-rearranged lung cancers, reporting the outcomes of the patients treated with the different therapies, focusing on multi-TKIs. This global multicenter registry involved a multicenter network of thoracic oncologists including 165 patients with a diagnosis of NSCLC from first to advanced stage. RET rearrangement was performed in an accredited local laboratory. Patients received a multi-TKI among alectinib, caboazontinib, lenvatinib, nintedanib, ponatinib, regorafenib, sorafenib, sunitinib, and vandetanib, at the dosage of these drugs as registered and currently used in their respective cancer indications. Patients were enrolled in the period between June 2015 and April 2016, in Europe, Asia, and USA. Median age of the patients was 61 years (range, 29 to 89 years), with a good balance between male and female patients. Sixty-three percent of patients were never-smokers. The most frequent histology was adenocarcinoma (98%), and the 72% of patients had an advanced disease at diagnosis. Molecular testing for RET was carried out locally by fluorescence in situ hybridization, next-generation sequencing, and real-time polymerase chain reaction. RET fusions were identified in 49% of cases. The most frequent fusion was KIF5B and was detected in 58 patients (72%), then CCDC6 in 19 patients (23%), NCOA4 in 2 patients (2%), EPFA5 and PICALM each in 1 patient (1%).

The median line of therapy with multi-TKI was third line setting (range first to eight lines). Among the 53 patients treated, 21 of them received caboazontinib, 11 patients received vandetanib, 10 sunitinib. Sorafenib, alectinib, lenvatinib, nintedanib and ponatinib were administered each to 2 patients, while only 1 patient received regorafenib. Responses to therapy were reported with caboazontinib, vandetanib, sunitinib, lenvatinib, and nintedanib. Objective response (OR) rate was observed in 13 (26%) of cases. Complete response (CR) was reported in 2 patients (4%), one with caboazontinib and one with nintedanib, respectively. PR was reported in 11 patients (22%), SD in 16 patients (32%), while 40% of patients progressed during single-agent RET inhibition therapy. Median progression free survival (PFS) was 2.3 months (95% CI: 1.6–5.0 months), and median overall survival (OS) was 6.8 months (95% CI: 3.9–14.3 months). The longer median PFS was reported with caboazontinib (3.6 months, 95% CI: 1.3–7.0 months), while the longer median OS was reported with vandetanib (10.2 months, 95% CI: 2.4–not reached). Regarding the various RET fusions, there were no statistically significant differences regarding PFS or OS.

Despite all the limits of retrospective data and uncontrolled drug dosage, the activity of caboazontinib reported in the present study is comparable to that reported for patients with RET fusions positive NSCLC in the ongoing phase 2 study of Drilon and colleagues, whose primary endpoint was overall response rate (ORR) (16). In this study, 26 patients received caboazontinib at 60 mg daily dosage, but 19 of them (73%) reduced the dose for drug-related adverse events (AEs). Response-assessable patients were 25, and 7 of them showed a confirmed PR (ORR 28%; 95% CI: 12–49). Median PFS was 5.5 months. The most frequently reported grade 3 treatment-related AEs were lipase elevation in 4 (15%) patients, and increased alanine aminotransferase and aspartate aminotransferase, decreased platelet count, and hypophosphatemia each one in 2 (8%) patients. Similarly, the findings reported with vandetanib are comparable with those from a study conducted in Korean patients (17) but inferior than results...
from another study conducted among Japanese patients (18). However, data derived from all these studies should be considered with caution, because of the rarity of RET fusions and the consequent small number of patients with these alterations and eligible to a multi-TKI treatment. Moreover, the wide spectrum of toxicity of the multi-TKIs should be considered.

From the global RET registry (15), we learn that among the 84 patients who received a platinum-based chemotherapy as first-line treatment, 65 were evaluable and 33 of them reported an OR (51%; 95% CI: 38.1–63.4). Median PFS was 7.8 months (95% CI: 5.3–10.2 months) and median OS was 24.8 months (95% CI: 13.6–32.3 months). Among 84 patients receiving chemotherapy, 66 of them received chemotherapy with platinum and pemetrexed.

The probable durable benefit with pemetrexed-based chemotherapy in NSCLC with RET rearrangements was already demonstrated in a retrospective review regarding patients treated at a single oncologic centre between 2007 and 2014. This analysis has some limitations as the fact that there was no standardized schedule of tumor assessments and patients with select driver-positive NSCLCs were taken as control groups that may not be representative of the overall of patients whose carcinomas are negative for RET rearrangements (19). However, the authors reported an ORR of 45% compared to an attested response rate of 30% with other platinum-based chemotherapy. Disease control was durable, with a median PFS of 19 months (95% CI: 12–not reached), and time to treatment discontinuation was prolonged.

Several elements should be taken into account to explain the efficacy of pemetrexed reported in this group of RET-rearranged NSCLC, as the fact that prolonged survival may reflect the natural history of these tumors, and that benefit due to pemetrexed-based chemotherapy may be reflective of the benefit with chemotherapy in general. Moreover, while the sensitivity of ALK-rearranged NSCLC to pemetrexed has previously been attributed to lower levels of thymidylate synthase compared to tumors without ALK fusions (20), we do not know yet the biologic explanation in support of the hypothesis of the probable increased activity of pemetrexed-based chemotherapy in RET-rearranged NSCLC. Future investigation is warranted.

In conclusion, we are facing lung cancer with RET rearrangement as a set of “rare tumors”. It is getting harder to conduct perspective trials with larger sample size, with at least two consequent questions: if for tumor subgroups, clinical trial should be conducted similar to those for frequent tumors, and how much and what evidence is needed to introduce a new treatment in clinical practice.

Although data from the present study (15) can have many limitations, on the other hand systematically examining the activity of multi-tyrosine inhibitors helped to better investigate a therapeutic option for patients with a RET-rearranged NSCLC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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