stopped for tumor progression. In May 2014, she was referred to our early-phase-trial unit for a possible inclusion in a phase I trial. Next-generation sequencing-based molecular screening of retro-pectoral metastasis identified an ERBB2 L869Q as well as a CDH1 R63* mutations, without ERBB2 amplification. Treatment by lapatinib (1250 mg/day continuously) and capicitabine (2000 mg/m² of body surface area on days 1–14 of a 21-day cycle) was initiated. At initiation, liver transaminase levels were 329 IU/l (aspartate transaminase) and 298 IU/l (alanine transaminase), CA15-3 marker was 3327 U/ml. After 4 months, transaminase levels and CA15-3 marker decreased dramatically (Figure 1A) and remain normal after 8 months. We also observed shrinkage of liver metastasis (Figure 1B–E). Nine months after the treatment onset, the patient is well and remains on treatment.

ILC represents 10% of breast cancers and differs from ductal carcinoma by the loss of E-cadherin function and lower ERBB2-amplification rate [3]. E-cadherin loss can be due to CDH1 mutation, which is observed in up to 83% of ILCs [3]. Interestingly, Ross et al. described an 18% of ERBB2 mutations (4/22) in CDH1-mutated metastatic ILC [4]. In another cohort, concomitant ERBB2 and CDH1 mutations occurred in 9% (3/36) [1]. For reasons not yet known, ERBB2 mutation rate seems to be higher in CDH1-mutated ILC than in non-CDH1-mutated breast cancer [1].

The ERBB2 L869Q mutation, located on the tyrosine kinase domain, has never been reported in breast cancer. It seems to be a CDH1 R63* mutations, without ERBB2 amplification. Treatment by lapatinib (1250 mg/day continuously) and capicitabine (2000 mg/m² of body surface area on days 1–14 of a 21-day cycle) was initiated. At initiation, liver transaminase levels were 329 IU/l (aspartate transaminase) and 298 IU/l (alanine transaminase), CA15-3 marker was 3327 U/ml. After 4 months, transaminase levels and CA15-3 marker decreased dramatically (Figure 1A) and remain normal after 8 months. We also observed shrinkage of liver metastasis (Figure 1B–E). Nine months after the treatment onset, the patient is well and remains on treatment.

The ERBB2 L869Q mutation, located on the tyrosine kinase domain, has never been reported in breast cancer. It seems to be functionally analogous to the L861Q mutation of EGFR in lung carcinoma [5]. We found this ERBB2 mutation in both the primary tumor and metachronous metastatic samples suggesting its ‘driver’ role in oncogenesis. Moreover, in our patient, the specific targeting of ERBB2 with lapatinib induces a dramatic and durable response. Indeed, provided that the tumor previously became resistant to capicitabine, the tumor response observed here is in favor of anti-HER2 activity of lapatinib.

The impressive response to anti-HER2 therapy observed here warrants an evaluation of the ERBB2 mutational status in all cases of ILC associated with CDH1 aberation. In this regard, results of the current clinical trial assessing neratinib in ERBB2-mutated breast cancer (NCT01670877) are awaited with great interest.

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Two cases of EGFR mutation-positive lung adenocarcinoma that transformed into squamous cell carcinoma: successful treatment of one case with rociletinib

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are highly effective for treatment of non-small cell lung cancer (NSCLC) harboring activating EGFR mutations. However, most treated patients develop resistance to these drugs, with mechanisms of such resistance including a secondary T790M mutation of EGFR, MET amplification, epithelial-to-mesenchymal transition, and histological transformation to small cell lung cancer (SCLC) [1].

A 48-year-old nonsmoking woman (case 1) was diagnosed with stage IIIA adenocarcinoma of the left lung positive for an exon 19 deletion of EGFR. She underwent adjuvant chemotherapy but experienced recurrence as lung metastases. She was then treated with gefitinib for 2 years and platinum-based chemotherapy for 6 months. After subsequent disease progression, rebiopsy of the lesions revealed histological transformation to squamous cell carcinoma (SCC) with the same EGFR mutation (Figure 1A). She died soon thereafter as a result of disease progression.

A 64-year-old nonsmoking woman (case 2) was diagnosed with stage IV adenocarcinoma of the right lung with lung metastases. Genetic analysis detected both L858R and T790M mutations of EGFR. Gefitinib and several cytotoxic agents were administered, but the patient experienced disease progression. Rebiopsy of the tumor revealed transformation to SCC with the identical EGFR mutations (Figure 1B). Administration of rociletinib, a third-generation EGFR-TKI, resulted in marked tumor regression (Figure 1C), and the patient was well managed with this drug for 10 months.

We thus report two cases of histological transformation from adenocarcinoma to SCC after EGFR-TKI treatment. Case 1 died soon after the transformation, whereas case 2, who harbored the T790M mutation of EGFR, was successfully treated with rociletinib.
Transformation from adenocarcinoma to SCC was recently described as a mechanism of acquired resistance to EGFR-TKIs in four patients [2–4]. These patients were initially well managed with a first-generation EGFR-TKI, but they eventually became EGFR-TKI resistant and died soon after the histological transformation. The mechanism of such histological transformation is unclear, but it is possible that the tumor is initially a mixed histological type such as adenosquamous carcinoma and that only the SCC component remains after EGFR-TKI treatment. In our cases, histological evidence of adenosquamous carcinoma was not apparent in the small tissue specimens obtained at the initial transbronchial biopsy. Another possibility is that transformation results from molecular changes in tumor stem cells associated with EGFR-TKI treatment, as has been suggested for the transformation of adenocarcinoma to SCLC [1]. Although loss of retinoblastoma 1 (RB1) was associated with the SCLC transformation [1], we did not detect loss of RB1 expression by immunohistochemistry in our two cases (data not shown).

SCC with activating EGFR mutations has been found to respond less well than adenocarcinoma to gefitinib [5]. Our case 2 harbored the T790M mutation and showed a durable response to rociletinib. As far as we are aware, this is the first reported case of histological transformation from adenocarcinoma to SCC that preserved the T790M mutation and was successfully treated with a third-generation EGFR-TKI. Our observations suggest that third-generation EGFR-TKIs are a potential treatment for SCC derived from adenocarcinoma and harboring T790M.

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references

A rational approach for salvage of testicular cancer patients

For both poor-prognosis patients and high-risk patients with primary mediastinal nonseminomatous germ-cell tumor (GCT), salvage therapy using high-dose chemotherapy (HDCT) with stem-cell transplant seems to be more effective than standard doses to achieve cure. This approach, however, does not prevent the emergence of resistance and, for most patients, disease progresses again.

In a recent article published in *Annals of Oncology*, which we have read with great interest, Nieto et al. [1] combined HDCT with the antivascular endothelial growth factor (VEGF) antibody bevacizumab, in an effort to improve outcomes. Two sequential HDCT cycles were used: bevacizumab/gemcitabine-docetaxel-melphalan-carboplatin and bevacizumab/ifosfamide-carboplatin-etoposide.

Bevacizumab was administered before chemotherapy. This treatment schedule explored the properties of bevacizumab to improve drug delivery through normalization in tumor vasculature.

Indeed, within solid tumors, the aberrant structure and function of tumor vessels creates a particularly chaotic microenvironment. The abnormal tumor vessel hyperpermeability leads to leaking of plasma proteins and fluid into the tumor interstitium which results in a marked elevation of the intratumoral pressure [2]. This increased intratumoral fluid pressure leads to a decreased transcapillary transport and a decreased drugs uptake.

The inhibition of VEGF can reduce tumor vessel permeability, remodeling the tumor vasculature and restoring the tumor interstitial pressure. In their work, Nieto et al. [1]rationally explored this property of bevacizumab to subsequently administrate intensive doses of chemotherapy trying to achieve minimal residual disease.

In addition, they consider the biological features of testicular GCT in respect to DNA repair proteins expression. In their first cycle of HDCT, gemcitabine is used to inhibit the nucleotide excision repair (NER), the main DNA repair pathway associated with cisplatin resistance in GCTs [3]. Indeed, GCT-resistant cells show high expression of XPF-ERCC1, protein implicated in both NER and interstrand cross-link repair, key pathways involved in the repair of cisplatin-induced lesions [4].

Reduction of the interstitial pressure is, however, a transient event which depends on the optimal dosing and scheduling of the antiangiogenic agent.

One might thus hypothesize that the second administration of bevacizumab done in their trial acts through a sustained inhibition of VEGF, blocking angiogenesis and increasing the intratumoral hypoxia. Hypoxia, then, induces the downregulation of homologous recombination (HR) genes such as BRCA1 and RAD51. This associated with the naturally weak HR repair capability in testicular GCT [5] is likely to contribute in explaining the synergistic increased sensitivity of these tumors to alkylating agents combined to bevacizumab.

Using this approach, Nieto et al. exceeded the previously published results using HDCT. The progression-free survival and overall survival rates were 55.8% and 58.1%, respectively, with a median follow-up of 46 months.

As the authors, we consider that mechanistically deciphering both disease etiology and drug resistance is crucial for developing more efficient trials using HDCT. Through a similar salvage strategy, our group, supported by the French Ministry of Health, is carrying out the TAXIF III study (ClinicalTrials.gov Identifier NCT01966913) where, besides the clinical approach, we aim at identifying predictive biomarkers to monitor and select patients most likely to benefit from the therapy.

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references

More on sunitinib 2 weeks on/1 week off schedule: the Rainbow analysis
We read with great interest the recent Rainbow study by Bracarda et al. [1]. This is the largest retrospective analysis