Clinical Response to a Lapatinib-Based Therapy for a Li-Fraumeni Syndrome Patient with a Novel HER2V659E Mutation

Violeta Serra, Ana Vivancos, Xose S. Puente, Enriqueta Felip, Daniel Silberschmidt, Ginevra Caratù, Josep-Lluís Parra, Leticia De Mattos-Arruda, Judit Grueso, Javier Hernández-Losa, Joaquín Arribas, Ludmila Prudkin, Paolo Nuciforo, Maurizio Scialtriti, Joan Seoane, and José Baselga

ABSTRACT
Genomic characterization of recurrent breast and lung tumors developed over the course of 10 years in a 29-year-old patient with a germline TP53 mutation (Li-Fraumeni Syndrome) identified oncogenic alterations in the HER2 and EGFR genes across all tumors, including HER2 amplifications, an EGFR-exon 20 insertion, and the first-in-humans HER2V659E mutation showing a phenotypic convergent evolution toward HER2 and EGFR alterations. Following the identification of HER2-activating events in the most recent lung carcinoma and in circulating tumor cells, we treated the reminiscent metastatic lesions with a lapatinib-based therapy. A symptomatic and radiologic clinical response was achieved. HER2V659E sensitivity to lapatinib was confirmed in the laboratory.

SIGNIFICANCE: The precise knowledge of the genomic alterations present in tumors is critical to selecting the optimal treatment for each patient. Here, we report the molecular characterization and clinical response to a lapatinib-based therapy for the tumors of a Li-Fraumeni patient showing prevalence of HER2 and EGFR genomic alterations.

INTRODUCTION
We describe the case of a 29-year-old nonsmoker female who, in 2003, underwent a bilateral mastectomy due to a malignant phyllodes tumor (MPT) and to a bilateral ductal carcinoma in situ (DCIS; Fig. 1A). The patient was treated with adjuvant tamoxifen from 2003 until 2008 (Fig. 1B). In November 2007, a nodule in the lower lobe of the left lung was detected in a control chest X-ray and was confirmed by computed tomography (CT) scan. A CT-guided needle aspiration of the lesion showed positivity for CK7 and TTF1, suggesting a primary lung adenocarcinoma. A left lower lobectomy and lymphadenectomy was subsequently performed and the pathology analysis showed a moderately differentiated invasive lung adenocarcinoma with a bronchioloalveolar pattern [non–small cell lung carcinoma

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A Tumor sites

B Treatment timelines

Figure 1. Tumor sites and treatment timelines. A, the different tumor localization for the MPT of 2 cm, the right DCIS of 1 cm (pT1mic, grade 3) and the left DCISs of 0.8 and 1 cm (pTis, grade 3), the non–small cell lung carcinoma (NSCLC) of the left lung of 1.6 cm (pT2N1), and the NSCLC of the right lung of 1 cm (T1N2M1). The pulmonary lymphangitic carcinomatosis (PLC) and the pleural effusion (PE) were not measurable. The hilar lymph nodes N1(10) (n = 2, of 0.5 cm), peribronchial N1(12) (n = 1, of 1 cm), subcarinal N2(7) (n = 2, of 9 and 3 mm), and paratracheal N2(2R) (n = 2, of 1.6 and 1 cm), N2(4R) (n = 1, of 3 cm), and N1(10) (n = 1, of 2 cm by CT scan) are also shown. B, the treatment timelines received by the patient. From 2003 until 2008, the patient received adjuvant tamoxifen (TAM). In 2008, following the lobectomy she received six cycles of cisplatin/docetaxel (CDDP/DOC). After the segmentectomy in 2012, she received two cycles of cisplatin/pemetrexed (CDDP/PM). On the basis of the identification of HER2-V659E, she received Lap/T (oral daily lapatinib 1,000 mg/ intravenous weekly paclitaxel 80 mg/m²).

(NSCLC) left with visceral pleural invasion and involvement of three N1 lymph nodes without N2 involvement (pT2N1). The patient received four cycles of postoperative adjuvant cisplatin/docetaxel chemotherapy. In December 2011, a follow-up CT scan detected a 1-cm nodule in the right lower lobe of the lung. In parallel, the left lung images could not rule out the presence of pulmonary lymphangitic carcinomatosis (PLC). A segmentectomy of the right lower lung lobe and lymph node sampling was performed, showing a 1-cm TTF1⁺ invasive adenocarcinoma (suggesting lung carcinoma origin, NSCLC right) and extensive invasion of N2 lymph nodes in the 2R, 4R, and 7 regions [N2(2R), N2(4R), and N2(7)]. Given the pattern of tumors developed by the patient, genetic counseling was provided and revealed that the patient carried a TP53R248W germline mutation, leading to the diagnosis of Li-Fraumeni Syndrome (LFS).

A postoperative CT scan confirmed the presence of PLC in the left lung, and the patient started cisplatin/pemetrexed chemotherapy. After two chemotherapy cycles, the patient reported the appearance of pain in the lower left thorax, and a CT scan showed the presence of a new pleural effusion in the left lung, a 2-cm nodule in the left hilus, and the previously detected PLC. As a result of whole-exome sequencing of her most recent tumor, the NSCLC right, an activating mutation HER2V659E was identified (Fig. 2). This result led us to consider that the tyrosine kinase inhibitor lapatinib could be a beneficial treatment option. Although this clinical decision was hypothesis-driven, we confirmed that HER2V659E-expressing cells were sensitive to lapatinib (Fig. 3). Lapatinib was given daily at a dose of 1,000 mg in combination with paclitaxel 80 mg/m². Shortly after starting therapy, the patient experienced pain relief at the lower left thorax and a pronounced improvement in breathing. Two months after the beginning of the treatment, a CT scan revealed a reduction in the pleural effusion in addition to shrinkage of the nodule in the left hilus (Fig. 4). Three months after the beginning of the lapatinib/paclitaxel treatment, the administration of paclitaxel was discontinued because of toxicity. Treatment with lapatinib continued, and trastuzumab, an anti-HER2 antibody, was added (initial dose of 8 mg/kg intravenously, followed by 6 mg/kg every 3 weeks). The observation that HER2 was amplified in circulating tumor cells (CTC) at this point in time, in addition to reports describing the clinical benefit of trastuzumab in the context of HER2-mutant NSCLC, supported this therapeutic approach (1, 2). The disease was further stabilized for an additional 6 months. In total, the clinical benefit lasted over 9 months.
Molecular characterization of the tumors.

Figure 2. A, the estrogen receptor (ER), progesterone receptor (PR), HER2, EGF receptor (EGFR), and PTEN levels were quantified by immunohistochemistry (IHC) or FISH. ND, not determined. B, exome sequencing analysis in five tumor samples. Blue represents mutations and yellow insertion–deletion alterations. In bold, Cancer Gene Census–annotated genes.

\[ H \text{score} = (0 \times \text{percentage of unstained cells} + 1 \times \text{percentage of weakly stained cells} + 2 \times \text{percentage of moderately stained cells} + 3 \times \text{percentage of strongly stained cells}). \]

For PTEN, the respective percentages are provided in parentheses. The table in C summarizes the HER family molecular alterations in the five tumors analyzed. Amp, amplification.

### RESULTS

**Molecular Characteristics of Tumors and CTCs**

To identify potential actionable mutations, molecular pathologic analysis and exome sequencing of the MPT, DCISs, NSCLCs, and N2(4R) were performed (Fig. 1A and B).

Tumors were analyzed for the expression level of HER2, EGF receptor (EGFR), estrogen receptor (ER), progesterone receptor (PR), and PTEN by immunohistochemistry (IHC), and HER2 and EGFR gene amplification by FISH (Fig. 2A). High expression of EGFR was found in the MPT and in the N2(4R). HER2 overexpression was observed in both DCISs by IHC, and HER2 gene amplification was confirmed by FISH. All three lung lesions showed Chr17 polysomy (the chromosome that bears HER2). HER2 gene amplification was observed in NSCLC right in 65% of tumor cells, whereas no amplification was found in NSCLC left. Interestingly, 23% of tumor cells presented HER2 amplification in N2(4R) (Supplementary Fig. S1). Similarly, CTCs exhibited HER2 gene amplification. PTEN (and PIK3CA later on) were assessed because of their potential negative predictive value toward HER2/EGFR therapy (3–6). Although PIK3CA was wild-type in all samples, PTEN expression displayed inter- and intratumoral heterogeneity (Fig. 2A).

Whole-exome sequencing was performed on DNA extracted from formalin-fixed paraffin-embedded (FFPE) tumor samples and from peripheral blood. We first identified the TP53-R248W mutation in the blood sample, confirming the diagnosis of LFS. However, the analysis of somatic variants presented two main difficulties. The percentage

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<table>
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<tr>
<th>Year</th>
<th>Tumor sample</th>
<th>Tumor area (%)</th>
<th>ER (%)</th>
<th>PR (%)</th>
<th>HER2 IHC</th>
<th>HER2 FISH ratio</th>
<th>Chr 17 polysomy</th>
<th>EGFR (H score)</th>
<th>PTEN (H score)</th>
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<td>MPT</td>
<td>80</td>
<td>ND</td>
<td>ND</td>
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<td>ND</td>
<td>ND</td>
<td>290</td>
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<td></td>
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<td>70</td>
<td>60</td>
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<td>No</td>
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<td>5</td>
<td>2</td>
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<td>4.15</td>
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<td>75</td>
<td>ND</td>
<td>ND</td>
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<td>1.11</td>
<td>Yes</td>
<td>130</td>
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<td>N2(4R)</td>
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<th>EGFR</th>
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<td>2008</td>
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<td>—</td>
<td>p.A767_S768insSVD</td>
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<td></td>
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<td>N2(4R)</td>
<td>20% cells Amp</td>
<td>p.A767_S768insSVD</td>
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Therapeutic Response to Novel HER2 Mutation

**A Biochemical activity of lapatinib**

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**B Antiproliferative activity of lapatinib**

![Graph showing antiproliferative activity of lapatinib](image)

Figure 3. **HER2**<sup>V659E</sup> response to lapatinib in MCF10A cells. **A**, MCF10A cells overexpressing empty vector control, HER2 wild-type, or HER2<sup>V659E</sup> were treated with increasing doses of lapatinib (0, 0.125, 0.5, and 2 μmol/L). Immunoblotting of the total and phosphorylated proteins was conducted. pERK, pAKT, and p4EBP1 are downstream biomarkers of HER2 activation. **B**, MCF10A cells overexpressing empty vector control, HER2 wild-type, or HER2<sup>V659E</sup> treated with increasing doses of lapatinib. Cell proliferation was superior in HER2<sup>V659E</sup>-overexpressing cells. Error bars indicate SD of six independent experiments. Patient plasma concentration of 2.43 μg/mL based on a 1,250 mg/daily dose.

of tumoral cells within the samples was diverse, and the tumor samples were fixed and conserved in paraffin for up to 10 years, generating DNA of variable quality. The analysis of MPT was not possible due to the low quality of the DNA, and for the other samples, a high number of otherwise low-frequency C>T/G>A transitions was detected. This likely represents cytosine deamination events caused by the fixation/storage of the sample (data not shown). Both factors prompted us to use stringent criteria for the identification of genomic alterations (Fig. 2B). Among the somatic mutations, we identified a transmembrane domain mutation of HER2, HER2-p.V659E (69% mutation allele frequency, MAF), in the NSCLC right. This mutation was a dinucleotide change [659 V(GTG)→E(GAA)] that has not been previously identified in human tumors and is orthologous to the well-described V(GTT)→E(GAA) that has not been previously identified in NSCLC right. This mutation was a dinucleotide change [659 V(GTG)→E(GAA)]. The high MAF of the HER2-p.V659E mutation was in agreement with the HER2 amplification identified by FISH. In addition, we identified an indel in exon 20 of *EGFR* [p.A766_A767insASV] (9), in the 2008 tumor, NSCLC left (25% MAF), which was also present in the N2(4R) lymph metastases (11% MAF). *EGFR* exon 20 insertions are infrequent, accounting for up to 4% of all *EGFR* mutations (9), and although no functional studies of our patient-specific *EGFR* indel have been reported, neighboring insertions positioned at the loop following the C-helix of EGFR (for example, p.M766_A767insASV) have been shown to be activating mutations, indicating that the insertion harbored by our patient is likely to result in constitutive receptor activation. HER2 and EGFR somatic mutations were confirmed by capillary sequencing (Supplementary Fig. S2B). Interestingly, all tumors presented alterations in either HER2 or EGFR, both members of the HER family of tyrosine kinase receptors (Fig. 2C). This indicates that HER-mediated signaling confers a selective advantage to the tumors and exemplifies a phenotypic convergent evolution toward a hyperactive HER pathway in all tumors of the LFS patient.

A comparison of the somatic mutations and indels found in the five tumors analyzed showed that both DCISs were independent primary tumors, as they did not share any genomic alteration between them or with the rest of the tumors (Fig. 2B and Supplementary Table S1). However, the analysis of the NSCLCs and the N2(4R) metastasis showed that these three samples were related. In support of this assessment, the NSCLC left and the N2(4R) shared five indels (including *EGFR* p.A767_S768insSVD) and two nonsynonymous mutations, indicating that N2(4R) is a metastasis derived from the NSCLC left. On the other hand, N2(4R) and NSCLC right contained cells with HER2 amplification and, moreover, both NSCLCs shared one indel as well as polysomy of chromosomes 14, 16, and 17 (Supplementary Fig. S3A and S3B). These results suggested a phylogenetic relationship between them.
The identification of the *HER2*\(^{V659E}\) in the most recent tumor prompted us to consider a therapeutic approach based on lapatinib. Studies using the MMTV-c-neu mouse model (a mouse model for breast cancer generated by the overexpression of the rat ortholog of *HER2*\(^{V659E}\)) have shown evidence of the antitumor activity of lapatinib (10, 11).

We decided to functionally validate the sensitivity of *HER2*\(^{V659E}\) to lapatinib in a preclinical *in vitro* model. *HER2*\(^{V659E}\) was overexpressed in MCF10A cells and, as expected, high levels of *HER2*\(^{V659E}\) led to hyperphosphorylation of the receptor and activation of the downstream signaling (Fig. 3A). Lapatinib inhibited *HER2*\(^{V659E}\) and EGFR signaling in a dose-dependent manner. At low concentrations of lapatinib the *HER2*\(^{V659E}\)-mutant cells were less sensitive to treatment than control cells, suggesting that the mutation could confer resistance to the treatment under these conditions, an observation that was extended to other EGFR/HER2–targeting agents (Supplementary Fig. S4). Importantly, when the inhibitor was used at a clinically achievable concentration of 2 \(\mu\)mol/L (12), MCF10A-expressing *HER2*\(^{V659E}\) exhibited the same sensitivity to lapatinib as control cells (Fig. 3B). This reinforced our hypothesis that lapatinib at clinically achievable concentrations could be beneficial for the patient.

**DISCUSSION**

The identification of tumor driver genetic alterations, like the ones observed in the HER family of tyrosine kinase receptors, has led to novel therapeutic approaches that have dramatically improved patient outcomes. The paradigmatic example is the discovery of *HER2* gene amplification in breast cancer and the clinical response of *HER2*-amplified tumors to the anti-HER2 monoclonal antibody trastuzumab (13, 14). In addition to trastuzumab, the tyrosine kinase inhibitor lapatinib has also been approved as the therapy for *HER2*-amplified tumors, thanks to its ability to reversibly inhibit the intracellular tyrosine kinase activity of HER2 and downstream pathways, such as phosphoinositide 3-kinase (PI3K)/AKT and extracellular signal–regulated kinase (ERK; refs. 15, 16).

In addition to *HER2* gene amplification, recent studies have shown that the *HER2* gene can also be altered by somatic gene point mutations and insertions and deletions (indels;...
Therapeutic Response to Novel HER2 Mutation

In summary, the thorough molecular characterization of tumors from a patient with LFS has led to the identification of alterations in HER2 and EGFR, among those the first-in-humans HER2V659E mutation. The genomic characterization of the patient, together with the preclinical analysis showing that cells bearing the HER2V659E mutation remain sensitive to clinically achievable doses of lapatinib, supported a lapatinib-based treatment for our patient. Notably, this therapeutic regimen led to clinical benefits with an objective decrease in tumor size and pleural effusion, relief of thoracic pain, and breathing improvement. The potential role of HER tyrosine kinase inhibitors in the therapy for HER2-mutant tumors deserves a systematic evaluation; therefore, a clinical trial with the irreversible HER2 inhibitor neratinib in metastatic breast cancer is currently under way (NCT01111825), and a “basket” clinical trial in patients with HER2 mutations from any other histologic origin is also in an advanced planning stage.

METHODS

The patient provided written informed consent for somatic and germline DNA analysis. FFPE tumor samples from six primary tumors, including a MPT, two DCISs (right and left), two NSCLCs (left and right), and one metastatic lymph node N2(4R), along with a blood sample from the patient were subjected to whole-exome sequencing. Samples were initially assessed for tumor content based on a hematoxylin and eosin staining (Fig. 2A). Genomic DNA was extracted from FFPE tumor samples using the DNA RecoverAll Total Nucleic Acid Isolation Kit for FFPE (Ambion) according to the manufacturer’s instructions. Germline DNA was extracted from whole blood using the QIAamp DNA Blood Midi Kit (Qiagen). Library preparation was performed following the standard Illumina protocol (Genomic Sample Prep) with slight modifications for FFPE-derived DNA samples. One microgram of DNA was decross-linked by heat incubation, fragmented, ends repaired, and an adenine was ligated to each of the 3′ ends, where sample-specific adaptors were linked. Libraries were amplified using eight to 12 cycles of PCR, and exome enrichment was performed using specific biotinylated probes (SureSelect XT Human All Exon 50Mb; Agilent). After enrichment, the exome libraries were PCR-amplified, quantified, and loaded in a HiSeq2000 sequencer (Illumina). Paired-end 100 base sequences were obtained and aligned to the reference genome using Burrows-Wheeler Aligner. This yielded a median depth of coverage in targeted regions between 13× and 80×, and with more than 83% of the exome having at least 10 reads. Tumor samples were compared with normal DNA as previously described (27). To remove artifacts likely caused by cytosine deamination due to fixation/long-term storage of FFPE samples, and due to the presence of a low tumor cell content of some samples, the following filtering criteria were applied: somatic variants were called when supported by at least three reads, representing at least 10% of the total reads and with a minimum coverage of 35×. Putative somatic mutations were manually inspected to remove false positives in homopolymer stretches and close to indels.

Disclosure of Potential Conflicts of Interest

J. Baselga is employed as a consultant at Novartis and Genentech. No potential conflicts of interest were disclosed by the other authors.

The Editor-in-Chief of Cancer Discovery (J. Baselga) is an author of this article. In keeping with the AACR’s Editorial Policy, the paper was peer reviewed and a member of the AACR’s Publications Committee rendered the decision concerning acceptability.
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**Development of methodology:** V. Serra, A. Vivancos, L. De Mattos-Arruda, J. Hernández-Losada, J. Baselga

**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** V. Serra, A. Vivancos, E. Felip, G. Caratú, L. De Mattos-Arruda, J. Grueso, J. Hernández-Losada, J. Arribas, L. Prudkin, P. Nuciforo, J. Baselga

**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** V. Serra, A. Vivancos, X.S. Puente, D. Silberschmidt, L. De Mattos-Arruda, J. Arribas, P. Nuciforo, J. Seoane, J. Baselga

**Writing, review, and/or revision of the manuscript:** V. Serra, A. Vivancos, E. Felip, L. De Mattos-Arruda, L. Prudkin, P. Nuciforo, M. Scaltriti, J. Seoane, J. Baselga

**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** V. Serra, J.-L. Parra, L. De Mattos-Arruda

**Study supervision:** V. Serra, J. Seoane, J. Baselga

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**REFERENCES**

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