Targeted Therapy for Patients with BRAF-Mutant Lung Cancer

Results from the European EURAF Cohort

Oliver Gautschi, MD, Julie Milia, PhD,† Bastien Cabarrou, MSc,‡ Marie-Virginia Bluthgen, MD,§ Benjamin Besse, MD,§ Egbert F Smit, MD,¶ Juergen Wolf, MD,‖ Solange Peters, MD-PhD,# Martin Früh, MD,** Dieter Koeberle, MD,†† Youssouf Oulkhouir, MD,‡‡ Martin Schuler, MD,§§ Alessandra Curioni-Fontecedro, MD,¶¶ Benjamin Huret, MD,‖‖ Mallorie Kerjouan, MD,## Sebastian Michels, MD,‖ Georg Pall, MD,*** Sacha Rothschild, MD-PhD,††† Gerald Schmid-Bindert, MD,‡‡‡ Matthias Scheffler, MD,‖ Rémi Veillon, MD,§§§ Luciano Wannesson, MD,¶¶¶ Joachim Diebold, MD,* Gérard Zalcman, MD,‖‖‖ Thomas Filleron, PhD,‡ and Julien Mazières, MD†*

*Tumorzentrum, Luzerner Kantonsspital, Luzern, Switzerland; †Hôpital Larrey, Centre Hospital-Universitaire, Université Paul Sabatier, Toulouse, France; ‡Institut Claudius Regaud IUCT-O, Toulouse, France; §Institut Gustave Roussy, Villejuif, France; ¶VU University Medical Center, Amsterdam, The Netherlands; ‖Center of Integrated Oncology Cologne, University Hospital Cologne, Cologne, Germany; #Centre Pluridisciplinaire d'Oncologie, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; **Onkologie/Hämatologie, Kantonsspital St. Gallen, St. Gallen, Switzerland; ††Medizinische Klinik, St. Claraspital, Basel, Switzerland; ‡‡Service de pneumologie et oncologie thoracique, Hopital Universitaire, Caen, France; §§University Hospital Essen, Essen, Germany; ¶¶University Hospital Zurich, Zurich, Switzerland; ‖‖Clinique Teissier, Valenciennes, France; ##Centre Hospitalier Intercommunal de Creteil, Créteil, France; ***University Hospital Innsbruck, Innsbruck, Austria; †††University Hospital Basel, Basel, Switzerland; ‡‡‡Heidelberg University Medical Center, Mannheim, Germany; §§§Hopital du Haut Lévèque, Pessac, France; ¶¶¶Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; and ‖‖‖Centre Hospitalier Universitaire, Université de Caen-Basse Normandie, Caen, France.

Disclosure: B. Besse received grants from GSK and Roche; A. Curioni received consulting fees from Roche and Boehringer-Ingelheim; J. Diebold received consulting fees from Pfizer and Roche; M. Früh received consulting fee from Roche; D. Koeberle received consulting fees From Merck and Lilly; S. Michels received: consulting fees from Novartis, Pfizer, and Boehringer-Ingelheim; G. Pall received travel grant and consulting fees from Roche and GSK; S. Rothschild received consulting fees from Lilly, BMS, Roche and Pfizer; M. Scheffler received consulting fees from BMS, Novartis, and Boehringer-Ingelheim; M. Schuler received consulting fees from AstraZeneca, Boehringer-Ingelheim, Celgene, Novartis, and Lilly and research grants from Boehringer Ingelheim and Novartis; R. Veillon received travel grant and consulting fees from Roche and Boehringer-Ingelheim; J. Wolf received consulting fees from AstraZeneca and Boehringer-Ingelheim; G. Zalcman received consulting fee from GSK. All other authors declared no conflicts of interest. The study was academic and not supported by industry.

This study was presented as a proffered paper at the International Association for the Study of Lung Cancer-European Society of Medical Oncology European Lung Cancer Conference on April 17, 2015 in Geneva.

Address for correspondence: Oliver Gautschi, MD, Medical Oncology, Department of Internal Medicine, Cantonal Hospital, 6000 Luzern, Switzerland, E-mail: oliver.gautschi@onkologie.ch

DOI: 10.1097/JTO.0000000000000625

ISSN: 1556-0864/15/1010-1451

Introduction: Approximately 2% of lung adenocarcinomas have BRAF (v-Raf murine sarcoma viral oncogene homolog B) mutations, including V600E and other types. Vemurafenib, dabrafenib, and sorafenib as BRAF inhibitors are currently tested in clinical trials, but access for patients is limited. The aim of this study was to document the clinical course of patients treated outside of clinical trials.

Methods: We conducted a retrospective multicenter cohort study in Europe of patients with advanced BRAF-mutant lung cancer treated with known BRAF inhibitors. Data were anonymized and centrally assessed for age, gender, smoking, histology, stage, local molecular diagnostic results, systemic therapies, and survival. Best response was assessed locally by RECIST1.1.

Results: We documented 35 patients treated in 17 centers with vemurafenib, dabrafenib, or sorafenib. Median age was 63 years (range 42–85); gender was balanced; 14 (40%) were never smokers; all (100%) had adenocarcinoma; 29 (83%) had V600E; 6 (17%) had other mutations; one of them had a concomitant KRAS mutation. Thirty (86%) patients had chemotherapy in the first line. Overall survival with first-line therapy was 25.3 months for V600E and 11.8 months for non-V600E. Thirty-one patients received one BRAF inhibitor, and four received a second inhibitor. Overall response rate with BRAF therapy was 53%, and disease control rate was 85%. Median progression-free survival with BRAF therapy was 5.0 months, and overall survival was 10.8 months.

Conclusions: These results confirm the activity of targeted therapy in patients with BRAF-mutant lung adenocarcinoma. Further trials are warranted to study combination therapies and drug resistance mechanisms.

Key Words: Lung cancer, Targeted therapy, BRAF, Vemurafenib, Dabrafenib.

(*J Thorac Oncol.* 2015;10: 1451–1457)

Lung cancer is the leading cause of cancer-related death in Europe.[1] The majority (80–90%) of patients with lung cancer are current or former smokers, and most (70%) patients present with advanced stage at the time of the diagnosis, where

palliative chemotherapy is the standard-of-care.[2] Prognosis remains poor, and new therapies are needed. Approximately 15–20% of Caucasian patients (mainly the never-smokers) have tumors harboring epidermal growth factor receptor (EGFR) mutations (10–13%) or anaplastic lymphoma kinase (ALK) rearrangements (3–7%) and can benefit from targeted therapy with oral tyrosine kinase inhibitors. Several EGFR and ALK inhibitors are approved, based on randomized clinical trials showing superiority over conventional chemotherapy.[3] Further potentially druggable targets include c-ros oncogene 1 (ROS1) and rearranged during transfection (RET) rearrangements, hepatocyte growth factor receptor (MET) amplification, and human epidermal growth factor receptor 2 (HER2) and BRAF (v-Raf murine sarcoma viral oncogene homolog B) mutations.[4] These alterations are less frequent (1–3%) than EGFR mutations or ALK rearrangements, and clinical experience with targeted therapy is often limited to case reports or small series.

The BRAF gene encodes the serine/threonine-protein kinase BRAF, which regulates normal cell growth and proliferation.[5] The kinase domain of BRAF is encoded by the amino acid residues 457–717. In the inactive conformation, the activation loop (residues 596–600) interacts with the P-loop, locking the kinase. Phosphorylation of the activation loop transforms the kinase into the active state, and B-Raf can activate the mitogen activated kinase-like protein (MAPK) signaling pathway.[6] BRAF is frequently mutated in cancer, with highest mutation rates in hairy cell leukemia (100%), malignant melanoma (>60%), and papillary thyroid cancer (>50%).[7–9] The most frequent BRAF mutation in cancer overall is V600E, leading to constitutive activation of B-Raf kinase and its downstream target extracellular regulated MAP kinase (ERK), whereas other BRAF mutations have also been described.[7] The clinical development of BRAF V600E specific small inhibitors was pioneered in the field of melanoma, with two drugs (vemurafenib and dabrafenib) approved for the treatment of patients with advanced disease.[10,11]

BRAF is mutated in 1% to 3% of lung cancers, predominantly in lung adenocarcinoma.[12–20] A large study by the U.S. Lung Cancer Mutation Consortium included 951 lung adenocarcinomas, 21 (2.2%) were BRAF-mutant, 17 of them had V600E, and 4 had non-V600E mutations.[20] We and others previously reported responses to vemurafenib in individual patients with BRAF-mutant lung cancer.[21–24] Dabrafenib induced responses in a phase I trial in patients with BRAF-mutant melanoma and other solid tumors, including lung cancer.[25] Sorafenib exceeded the prespecified efficacy end point (8-week disease control rate) in patients with Kristen rat sarcoma oncogene (KRAS) or BRAF mutant lung cancer in the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial.[26] However, clinical experience with BRAF inhibitors in patients with lung cancer remains limited. We conducted this study to collect and analyze data from patients with BRAF-mutant lung cancer receiving targeted therapy outside of a clinical trial.

PATIENTS AND METHODS

Patients and Ethical Considerations

Eligibility criteria for this study were diagnosis of non–small-cell lung cancer (NSCLC) by local pathology (all histological subtypes), advanced stages III and IV by the 7th TNM classification, BRAF mutation by local testing (including V600E and non-V600E), and at least one line of therapy with a commercial BRAF inhibitor. Local laboratories had to be accredited, quality controlled, and could use any established test method, including Sanger sequencing or next generation sequencing (NGS). Reports had to be available as written documents. Contributors were responsible for patient information, consent, and institutional review board approval, according to local regulations.

Treatment and Follow-up

Only patients treated with a BRAF inhibitor outside of a clinical trial were accepted in our study. Based on the regulatory situation in Europe in 2012–2014, commercially available BRAF inhibitors were vemurafenib, dabrafenib, and sorafenib. Patients treated with MEK inhibitors, or treated in clinical trials with BRAF or MEK inhibitors, were excluded from our study. Computed tomography scans were performed every 2–4 months. Brain imaging was done in the presence of symptoms, or in patients with known brain metastases.

Data Collection

Between October and December 2014, the study coordinator (J.M.) registered all patients in a central database and collected anonymized data from the participating centers, including patient characteristics (age at diagnosis, gender, smoking, survival status), tumor parameters (histology, stage at diagnosis, metastatic sites, BRAF mutation type), and systemic therapies (generic drug names, start date, end date, best response by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 on local assessment, duration of therapy). Unexpected or fatal adverse events were also noted. The database was updated in January and February 2015 and locked for the statistical analysis on February 28, 2015.

Statistics

All calculations were performed by independent statisticians (B.C. and T.F.). Categorical variables were presented as contingency tables, ie, number and percentage for each category of variable and number of missing data. Quantitative variables were presented as median, range, and missing data. Survival data were summarized by the Kaplan–Meier method with 95% confidence intervals. Progression-free survival (PFS) was defined as the time between the date of start of treatment (either chemotherapy or targeted anti-BRAF treatment) and the date of tumor progression or death. Patients alive and progression free at the date of the last follow-up were censored. Overall survival (OS) was defined as the time between the date of start of treatment (either chemotherapy or targeted–anti-BRAF treatment) and the date of death. Patients alive at the date of last follow-up were censored. The main endpoints of the study were overall response rate (ORR) and PFS for BRAF therapy. Statistical analysis was performed under STATA Version 13 software (Stata Corporation, College Station, TX).

TABLE 1. Patient Characteristics

Sample size (N)	35
Age at diagnosis	
Median years (range)	63 (42–85)
Gender	
Male	18 (51%)
Female	17 (49%)
Smoking status	
Never	14 (40%)
Former/current	16 (46%)
Unknown	5 (14%)
Country	
France	13 (37%)
Switzerland	10 (28%)
Germany	7 (20%)
The Netherlands	4 (11%)
Austria	1 (3%)
Systemic therapy	
Median lines (range)	3 (1–6)
Platinum-based frontline therapy	30 (86%)

RESULTS

Patient Characteristics and Tumor Parameters

We collected data from 35 eligible patients from 17 centers in five different countries, including France (13), Switzerland (10), Germany (7), the Netherlands (4), and Austria (1; Table 1). Median age was 63 years (range, 42–85 years); gender was balanced; 40% were never smokers; and 46% were current or former smokers. All (100%) patients had lung adenocarcinoma histology; 34 (97%) had advanced tumor stage (III/IV) at the time of initial diagnosis; 1 had early disease at the time of the initial diagnosis (Table 2). Ten patients had malignant effusion, and six had brain metastases. By definition, all patients had a BRAF mutation, 29 (83%) V600E, and 6 (17%) non-V600E, including G466V, G469A, G469L, G596V, V600K, and K601E. One (3%) patient had a co-occurring driver mutation, which was KRAS V12 together with BRAF V600K. Another patient had concomitant HER2 amplification with BRAF V600E. No co-occurring alterations of EGFR, ALK, MET, RET, or ROS1 were reported.

TABLE 2. Tumor Parameters

Sample size (N)	35
NSCLC histology	
Adenocarcinoma	35 (100%)
Other	0
Stage at initial NSCLC diagnosis	
I and II	1 (3%)
III	4 (11%)
IV	30 (86%)
Metastatic sites of special interest	
Malignant effusion	10 (29%)
Brain metastases	6 (17%)
BRAF mutation	
V600E	29 (83%)
Non-V600E	6 (17%): G466V, G469A, G469L, G596V, V600K, K601E
Other driver mutations	
No	34 (97%)
Yes	1 (3%): KRAS V12

NSCLC, non–small-cell lung cancer.

Drug Exposure

All 35 patients had at least one line of therapy with a known BRAF inhibitor (Table 3). Thirty-one patients received one BRAF inhibitor, and four patients received two different inhibitors, including three patients treated with vemurafenib followed by dabrafenib and one patient treated with sorafenib followed by vemurafenib. A total of 39 lines of BRAF-targeted therapy were administered, 29 with vemurafenib, nine with dabrafenib, and one with sorafenib. Drugs were prescribed at their registered dose, which was 960 mg twice a day for vemurafenib, 150 mg twice a day for dabrafenib, and 400 mg for sorafenib. Five patients had BRAF therapy in the first line (all with vemurafenib), 30 had BRAF therapy in further lines. Among the latter, all 30 had platinum-based first-line chemotherapy, 21 of them with pemetrexed, three with paclitaxel, three with vinorelbine, and three with gemcitabine. Five patients had bevacizumab in addition to chemotherapy. The median number of systemic therapies (including BRAF-targeted therapy) was three, and the maximum was six. No unexpected or fatal adverse effects were reported.

Best Response with Systemic Therapy

Best response was assessed locally by RECIST1.1 (Table 4). For BRAF therapy, one patient had missing response data and was excluded, 34 patients had data and were included in the analysis. Of the latter, one (3%) patient had nonmeasurable disease by response evaluation criteria in solid tumors two (6%) had complete response, 16 (47%) had partial response (PR), 11 (32%) had stable disease, and 4 (11%) had progressive disease. ORR was 53% (95% confidence interval [CI]: 35.1–70.2), and disease control rate (DCR) was 85% (95% CI: 68.9–95.0). In

TABLE 3. Drug Exposure

Sample size (N)	35
BRAF inhibitor therapy	35 (100%)
BRAF inhibitors and lines (total)	39
Vemurafenib	29
Dabrafenib	9
Sorafenib	1
Sequential BRAF inhibitors	
No	31 (89%)
Yes	4 (11%): 3× vemurafenib → dabrafenib and 1× sorafenib → vemurafenib
BRAF inhibitor used in	
First line	5 (14%)
Further lines	30 (86%)

TABLE 4. Best Response with BRAF Inhibitor

	All Patients (N = 35)	V600E and Vemurafenib Subgroup (N = 25)
Data missing	1	1
Not measurable	1 (3%)	1 (4%)
CR	2 (6%)	2 (8%)
PR	16 (47%)	11 (46%)
SD	11 (32%)	10 (42%)
PD	4 (12%)	0
ORR	18 (53%; 95% CI: 35–70)	13 (54%; 95% CI: 33–74)
DCR	29 (85%; 95% CI: 69–95)	23 (96%; 95% CI: 79–100)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate; CI, confidence interval.

the 24 evaluable patients with BRAF V600E and vemurafenib therapy, ORR was 54% (95% CI: 32.8–74.4) and DCR was 96% (95% CI: 78.9–99.9). Among the five patients with first-line vemurafenib therapy, three (60%) had a response. One patient received sorafenib in second line and had PR. Among the 4 patients with two BRAF-inhibitors, one (25%) had a PR with dabrafenib after vemurafenib. From the 6 patients with non-V600E, one (17%) with G596V had PR with vemurafenib. ORR with first-line chemotherapy was 38%, no remissions were seen with docetaxel or erlotinib used in further lines (data not shown).

Survival and Duration of Therapy

From the entire cohort, one patient had missing survival data, 34 (97%) patients were evaluable for PFS and OS. For first-line therapy, including chemotherapy, PFS was 37 weeks (9.3 months) for V600E and 6 weeks (1.5 months) for non-V600E (Fig. 1). OS was 101 weeks (25.3 months) for V600E and 47 weeks (11.8 months) for non-V600E. Logrank testing was not performed because of small sample size. For BRAF therapy, median PFS was 20 weeks (5.0 months; 95% CI: 12–41 weeks), and OS was 43 weeks (10.8 months; 95% CI: 22–96 weeks; Fig. 2). Duration of BRAF therapy was evaluable in 34 patients, with a median of 17 weeks (4.3 months; range, 2–164 weeks; Fig. 3). Some patients had response evaluation criteria in solid tumors responses within 3–4 months after start of BRAF-targeted therapy (Fig. 4).

DISCUSSION

The EURAF cohort confirmed the clinically relevant antitumor activity of vemurafenib and dabrafenib in patients with advanced BRAF-mutant lung cancer, consistent with preliminary reports from two phase II trials.[27,28] In the vemurafenib basket trial (VE-BASKET) trial (NCT01524978), patients with solid tumors or multiple myeloma and BRAF codon 600 mutation by local testing were treated with vemurafenib at the standard dose of 960 mg twice a day. So far, the investigators reported on 19 patients with lung cancer, of which eight (42%) had unconfirmed PR, and eight (42%) had stable disease, for an unconfirmed DCR of 84%.[27] The trial BRF113928 with dabrafenib enrolled 84 patients with lung cancer and V600E, ORR in second line was 32%, DCR was 56%, and PFS 5.2 months.[28] Publication of these trials in a peer-reviewed journal is pending. Another phase II trial, AcSé vemurafenib (NCT02304809), is currently enrolling further patients in France.

In the European BRAF cohort (EURAF) cohort, we observed rapid and marked tumor responses in some patients with heavy pretreatment and advanced age. Such patients are generally excluded from clinical trials. Consistent with our previous "real-world" cohorts European ROS1 cohort (EUROS1) and European HER2 cohort (EUHER2), these results suggested that patients treated outside of trials can derive similar benefit from molecular testing and targeted therapy, as patients treated within trials.[29,30] Moreover, EURAF included six patients with BRAF non-V600E mutations. Consistent with a recent U.S. study,[19] patients with non-V600E had shorter OS than patients with V600E in our cohort. All tumors with non-V600E mutations located outside of the activation segment of the BRAF kinase domain were refractory to BRAF therapy, including the one with G469L described previously.[31] One patient with G596V achieved PR with vemurafenib. Consistent with preclinical experiments with L597-mutant melanoma cells, this supported the notion that mutations located within the activation loop (codon 596 through 600) are potentially sensitive to

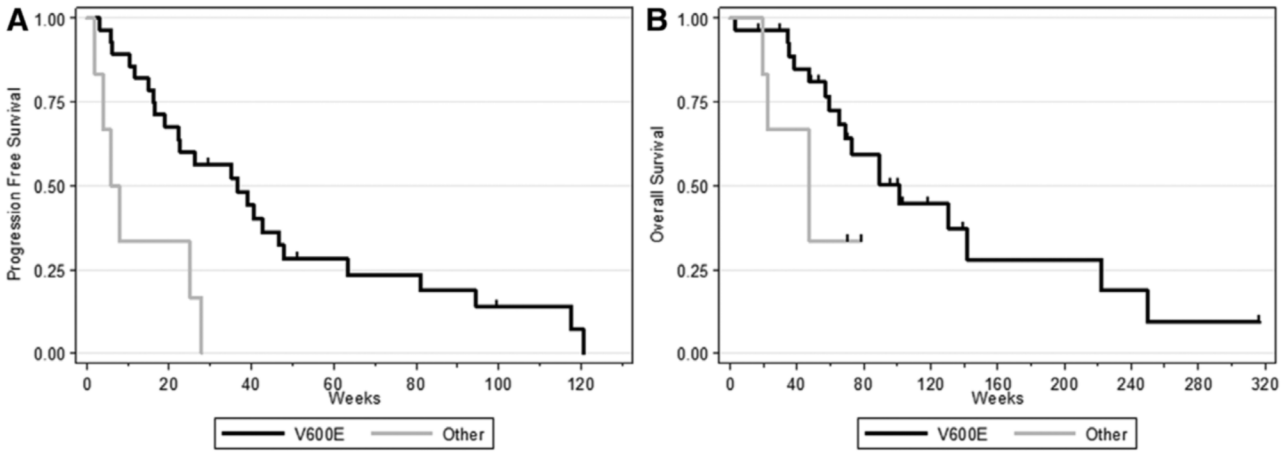

FIGURE 1. Survival from first-line therapy: (*A*) progression free survival; (*B*) overall survival.

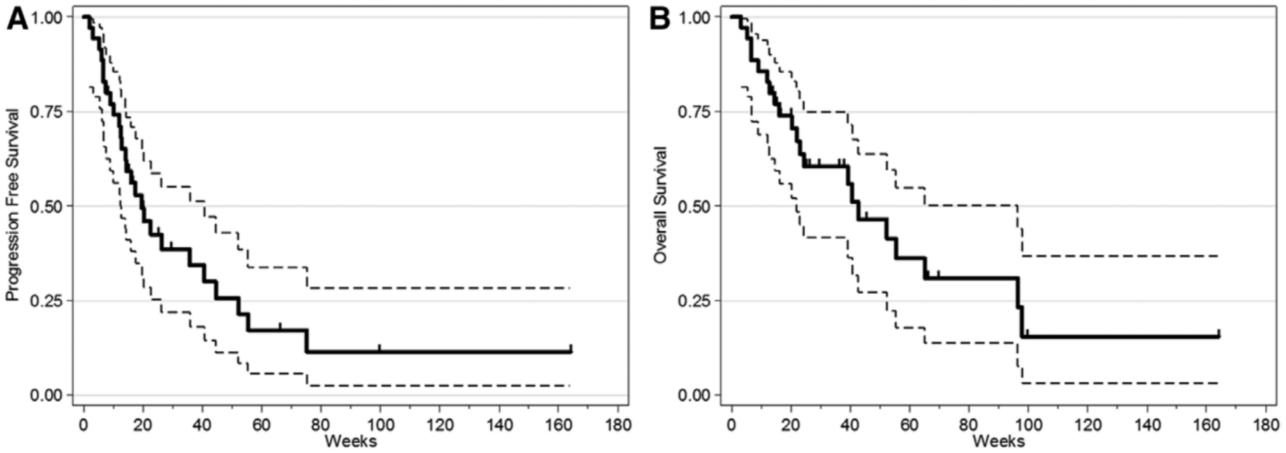

FIGURE 2. Survival with BRAF therapy: (*A*) progression free survival; (*B*) overall survival.

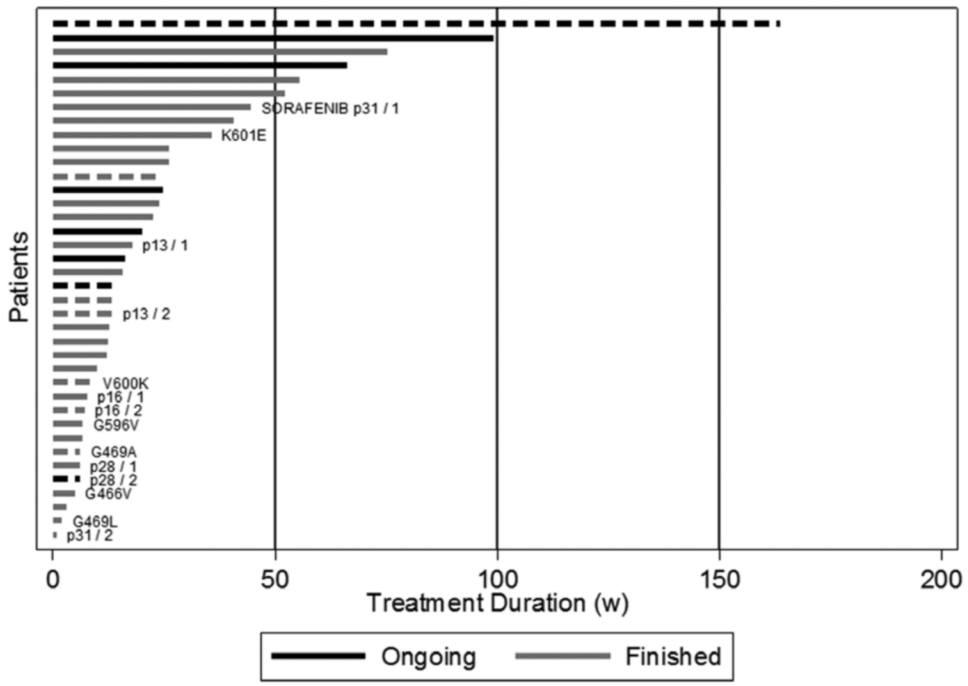

FIGURE 3. Duration of BRAF therapy. Legend: Bar colors indicate ongoing (black) or finished (grey) BRAF therapy. Continuous lines indicate vemurafenib, dashed lines dabrafenib. Patients treated with two different BRAF-inhibitors are depicted by their patient code (p#), each BRAF therapy is represented by a separate bar (#1 or #2). Only the non-V600E mutations are labeled, and all other patients had V600E.

BRAF inhibition.[32] Although the incidence of such mutations is rather low, further clinical research is needed.[19,20] Among the four patients in EURAF with two lines of targeted therapy, one had a response with dabrafenib after vemurafenib, as reported elsewhere.[24] Another group recently published a case with intracranial response, a finding which we did not observe, perhaps because (brain) imaging was not predefined in our retrospective study.[23] Other limitations of EURAF were lack of central testing and lack of independent radiological review. However, all participating centers had accredited diagnostic laboratories, and all evaluations were carried out by trained and experienced investigators.

As expected from the literature, EURAF included nonsmokers and smokers.[19,20] Compared with nonsmokers, BRAF (and MET) mutations in smokers are among the most frequent recurrent oncogenic drivers for which targeted therapy presently exist.[33] All patients in EURAF had adenocarcinoma histology, supporting the current recommendations for molecular testing of nonsquamous NSCLC.[4] Consistent with the Lung Cancer Mutation Consortium study, one (3%) patient in our study had two driver mutations in the same tumor.[20] In the initial bronchial biopsy, only the BRAF V600K mutation was detected by Sanger sequencing. When the patient received dabrafenib, the tumor progressed with

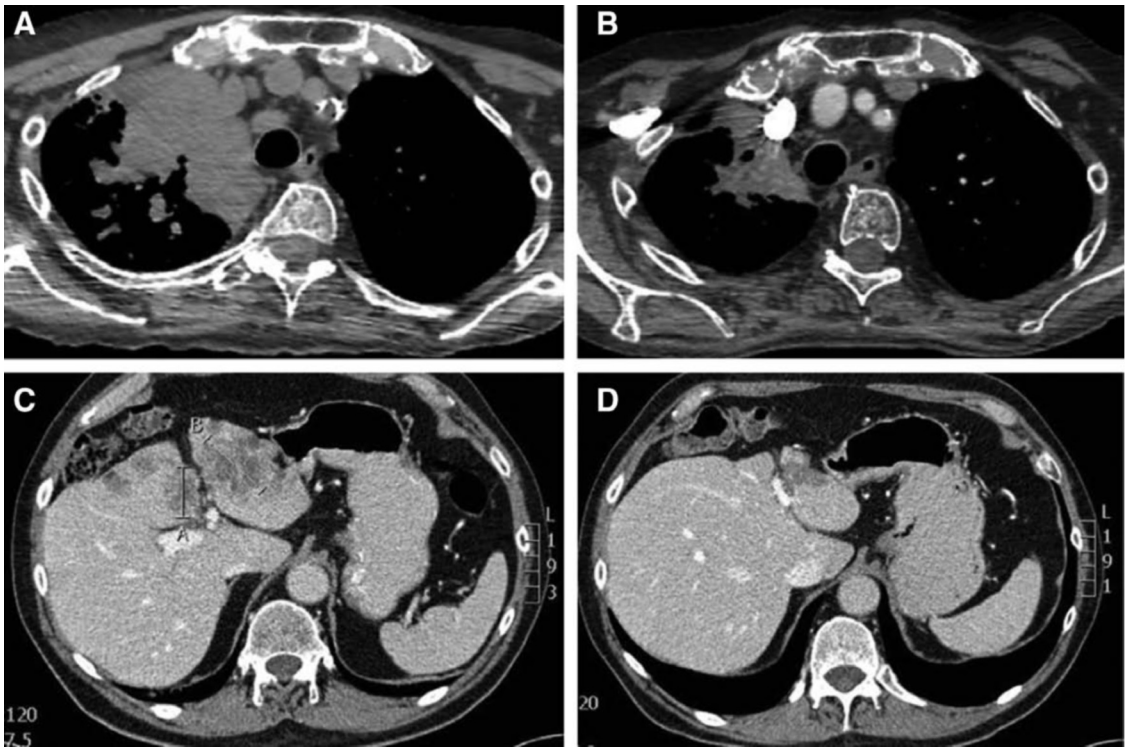

FIGURE 4. Patient examples. *A* and *C*, Baseline computed tomography scans of two different patients with lung adenocarcinoma and V600E. *B* and *D*, Follow-up computed tomography scans showing tumor remissions after 3 months of therapy with vemurafenib.

massive pleural effusion requiring repeated thoracocentesis. NGS on pleural tumor cells revealed a KRAS V12 mutation, which was also identified in the initial diagnostic sample by NGS, although with lower allele frequency. These observations may explain the lack of drug activity in a potentially sensitive tumor with V600K and were consistent with previous reports by others on the outgrowth of RAS-mutant clones under BRAF therapy and the superior sensitivity of NGS compared with Sanger sequencing.[34,35] Other mechanisms of resistance to BRAF inhibitors include EGFR upregulation and ERK/MEK pathway activation through CRAF.[36–38] In patients with melanoma, combined MEK and BRAF inhibition significantly prolonged survival, compared with BRAF-monotherapy.[39,40] In preclinical lung cancer models, combination was also more active than single agent.[41] A nonrandomized phase II trial with dabrafenib plus trametinib is currently recruiting patients with BRAF-mutant lung cancer (NCT01336634). Another approach to overcoming drug resistance in BRAF-mutant cancer is immune checkpoint inhibition.[42] In patients with melanoma, a phase I trial with targeted therapy plus immunotherapy is currently ongoing (NCT01656642). Because EGFR-mutant lung cancer cells have been shown to upregulate programmed death ligand 1 expression, such combination therapies should also be tested in patients with lung cancer and activating BRAF mutations.[43]

ACKNOWLEDGMENT

We thank all patients and their families for supporting this study. We also thank the following colleagues for their collaboration: Henning Burmeister from Switzerland, Federico Cappuzzo from Italy, Annemarie Dingemans from The Netherlands, Rafael Rosell and Natalie Karachaliou from Spain, and Eric Dansin, Pierre Fournel, Hérve Léna, Thierry Molina, Isabelle Monnet, Elisabeth Quoix, Nicolas Richard and Luc Thiberville from France.

REFERENCES

1. Malvezzi M, Bertuccio P, Rosso T, et al. European cancer mortality predictions for the year 2015: does lung cancer have the highest death rate in EU women? *Ann Oncol* 2015;26:779–786.
2. Reck M, Popat S, Reinmuth N, et al.; ESMO Guidelines Working Group. Metastatic non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2014;25 (Suppl 3):iii27–iii39.
3. Somasundaram A, Socinski MA, Burns TF. Personalized treatment of EGFR mutant and ALK-positive patients in NSCLC. *Expert Opin Pharmacother* 2014;15:2693–2708.
4. Horn L. Advances in the treatment of non-small cell lung cancer. *J Natl Compr Canc Netw* 2014;12(5 Suppl):764–767.
5. Sithanandam G, Druck T, Cannizzaro LA, Leuzzi G, Huebner K, Rapp UR. B-raf and a B-raf pseudogene are located on 7q in man. *Oncogene* 1992;7:795–799.
6. Pritchard AL, Hayward NK. Molecular pathways: mitogen-activated protein kinase pathway mutations and drug resistance. *Clin Cancer Res* 2013;19:2301–2309.
7. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. *Nature* 2002;417:949–954.
8. Wan PT, Garnett MJ, Roe SM, et al.; Cancer Genome Project. Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. *Cell* 2004;116:855–867.
9. Holderfield M, Deuker MM, McCormick F, McMahon M. Targeting RAF kinases for cancer therapy: BRAF-mutated melanoma and beyond. *Nat Rev Cancer* 2014;14:455–467.

10. Chapman PB, Hauschild A, Robert C, et al.; BRIM-3 Study Group. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 2011;364:2507–2516.
11. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet* 2012;380:358–365.
12. Marchetti A, Felicioni L, Malatesta S, et al. Clinical features and outcome of patients with non-small-cell lung cancer harboring BRAF mutations. *J Clin Oncol* 2011;29:3574–3579.
13. Kobayashi M, Sonobe M, Takahashi T, et al. Clinical significance of BRAF gene mutations in patients with non-small cell lung cancer. *Anticancer Res* 2011;31:4619–4623.
14. Paik PK, Arcila ME, Fara M, et al. Clinical characteristics of patients with lung adenocarcinomas harboring BRAF mutations. *J Clin Oncol* 2011;29:2046–2051.
15. Cardarella S, Ogino A, Nishino M, et al. Clinical, pathologic, and biologic features associated with BRAF mutations in non-small cell lung cancer. *Clin Cancer Res* 2013;19:4532–4540.
16. Barlesi F, Blons H, Beau-Faller M, et al.; Intergroupe Francophone de Cancérologie Thoracique (IFCT). Biomarkers (BM) France: results of routine EGFR, HER2, KRAS, BRAF, PI3KCA mutations detection and EML4-ALK gene fusion assessment on the first 10,000 non-small cell lung cancer (NSCLC) patients (pts). *J Clin Oncol* 2013;31 (suppl; abstr 8000).
17. Chen D, Zhang LQ, Huang JF, et al. BRAF mutations in patients with non-small cell lung cancer: a systematic review and meta-analysis. *PLoS One* 2014;9:e101354.
18. Kinno T, Tsuta K, Shiraishi K, et al. Clinicopathological features of nonsmall cell lung carcinomas with BRAF mutations. *Ann Oncol* 2014;25:138–142.
19. Litvak AM, Paik PK, Woo KM, et al. Clinical characteristics and course of 63 patients with BRAF mutant lung cancers. *J Thorac Oncol* 2014;9:1669–1674.
20. Villaruz LC, Socinski MA, Abberbock S, et al. Clinicopathologic features and outcomes of patients with lung adenocarcinomas harboring BRAF mutations in the Lung Cancer Mutation Consortium. *Cancer* 2015;121:448–456.
21. Gautschi O, Pauli C, Strobel K, et al. A patient with BRAF V600E lung adenocarcinoma responding to vemurafenib. *J Thorac Oncol* 2012;7:e23–e24.
22. Peters S, Michielin O, Zimmermann S. Dramatic response induced by vemurafenib in a BRAF V600E-mutated lung adenocarcinoma. *J Clin Oncol* 2013;31:e341–e344.
23. Robinson SD, O'Shaughnessy JA, Cowey CL, Konduri K. BRAF V600E-mutated lung adenocarcinoma with metastases to the brain responding to treatment with vemurafenib. *Lung Cancer* 2014;85:326–330.
24. Schmid S, Siano M, Joerger M, Rodriguez R, Müller J, Früh M. Response to dabrafenib after progression on vemurafenib in a patient with advanced BRAF V600E-mutant bronchial adenocarcinoma. *Lung Cancer* 2015;87:85–87.
25. Falchook GS, Long GV, Kurzrock R, et al. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial. *Lancet* 2012;379:1893–1901.
26. Kim ES, Herbst RS, Wistuba II, et al. The BATTLE trial: personalizing therapy for lung cancer. *Cancer Discov* 2011;1:44–53.
27. Hyman DM, Blay JY, Chau I, et al. VE-BASKET, a first-in-kind, phase II, histology-independent "basket" study of vemurafenib (VEM) in nonmelanoma solid tumors harboring BRAF V600 mutations (V600m). *J Clin Oncol* 2014;32:5s (suppl; abstr 2533)
28. Planchard D, Kim TM, Mazières J, et al. Dabrafenib in patients with BRAF V600E-mutant advanced non-small cell lung cancer (NSCLC): a multicenter, open-label, phase II trial (BRF113928*). Ann Oncol* 2014; 25:1–41.
29. Mazières J, Peters S, Lepage B, et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. *J Clin Oncol* 2013;31:1997–2003.
30. Mazières J, Zalcman G, Crinò L, et al. Crizotinib therapy for advanced lung adenocarcinoma and a ROS1 rearrangement: results from the EUROS1 cohort. *J Clin Oncol* 2015;33:992–999.
31. Gautschi O, Peters S, Zoete V, et al. Lung adenocarcinoma with BRAF G469L mutation refractory to vemurafenib. *Lung Cancer* 2013;82:365–367.
32. Dahlman KB, Xia J, Hutchinson K, et al. BRAF(L597) mutations in melanoma are associated with sensitivity to MEK inhibitors. *Cancer Discov* 2012;2:791–797.
33. Govindan R, Ding L, Griffith M, et al. Genomic landscape of non-small cell lung cancer in smokers and never-smokers. *Cell* 2012;150:1121–1134.
34. Drilon A, Wang L, Arcila ME, et al. Broad, hybrid capture-based next-generation sequencing identifies actionable genomic alterations in lung adenocarcinomas otherwise negative for such alterations by other genomic testing approaches. *Clin Cancer Res*. 2015 [Epub ahead of print].
35. Rudin CM, Hong K, Streit M. Molecular characterization of acquired resistance to the BRAF inhibitor dabrafenib in a patient with BRAF-mutant non-small-cell lung cancer. *J Thorac Oncol* 2013;8:e41–e42.
36. Prahallad A, Sun C, Huang S, et al. Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR. *Nature* 2012;483:100–103.
37. Johnson GL, Stuhlmiller TJ, Angus SP, Zawistowski JS, Graves LM. Molecular pathways: adaptive kinome reprogramming in response to targeted inhibition of the BRAF-MEK-ERK pathway in cancer. *Clin Cancer Res* 2014;20:2516–2522.
38. Lin L, Asthana S, Chan E, et al. Mapping the molecular determinants of BRAF oncogene dependence in human lung cancer. *Proc Natl Acad Sci U S A* 2014;111:E748–E757.
39. Larkin J, Ascierto PA, Dréno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med* 2014;371:1867–1876.
40. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med* 2015;372:30–39.
41. Joshi M, Rice SJ, Liu X, Miller B, Belani CP. Trametinib with or without vemurafenib in BRAF mutated non-small cell lung cancer. *PLoS One* 2015;10:e0118210.
42. Helissey C, Champiat S, Soria JC. Immune checkpoint inhibitors in advanced nonsmall cell lung cancer. *Curr Opin Oncol* 2015;27:108–117.
43. Chen N, Fang W, Zhan J, et al. Up-regulation of PD-L1 by EGFR activation mediates the immune escape in EGFR-driven NSCLC: implication for optional immune targeted therapy for NSCLC patients with EGFR mutation. *J Thorac Oncol*. 2015;10:910–923.

