**BRAF Alterations as Therapeutic Targets in Non–Small-Cell Lung Cancer**

Tu Nguyen-Ngoc, MD, PhD,* Hasna Bouchaab, MD,* Alex A. Adjeti, MD, PhD,† and Solange Peters, MD, PhD*

**Background:** Several subsets of non–small-cell lung cancer (NSCLC) are defined by molecular alterations acting as tumor drivers, some of them being currently therapeutically actionable. The rat sarcoma (RAS)–rapidly accelerated fibrosarcoma (RAF)–mitogen-activated protein/extracellular signal-regulated kinase kinase (MEK)–extracellular signal-regulated kinase (ERK) pathway constitutes an attractive potential target, as v-Raf murine sarcoma viral oncogene homolog B (BRAF) mutations occur in 2–4% of NSCLC adenocarcinoma.

**Methods:** Here, we review the latest clinical data on BRAF serine/threonine kinase inhibitors in NSCLC.

**Results:** Treatment of V600E BRAF-mutated NSCLC with BRAF inhibitor monotherapy demonstrated encouraging antitumor activity. Combination of BRAF and MEK inhibitors using dabrafenib and trametinib is under evaluation. Preliminary data suggest superior efficacy compared with BRAF inhibitor monotherapy.

**Conclusion:** Targeting BRAF alterations represents a promising new therapeutic approach for a restricted subset of oncogene-addicted NSCLC. Prospective trials refining this strategy are ongoing. Next step will probably aim at combining BRAF inhibitors and immunotherapy or alternatively improve a multilevel mitogen-activated protein kinase (MAPK) pathway blockade by combining with ERK inhibitors.

**Key Words:** BRAF, V600E, MEK, Vemurafenib, Dabrafenib, Trametinib, Non–small-cell lung cancer.

(J Thorac Oncol. 2015;10: 1396–1403)

Lung cancer is a leading cause of cancer death worldwide, with 1.6 million deaths annually. Environmental factors and genetic alterations seem to contribute to increase lung cancer risk. Although the majority of lung cancer cases is related to tobacco smoking, 10–30% occurs in light-smoker or never-smoker patients, with a higher proportion of light-smoker or never-smokers in Asian countries. Therapeutic decisions have traditionally been based on tumor histology. Non–small-cell lung cancer (NSCLC) accounts for 85% to 90% of lung cancers, with over 60% diagnosed at an advanced stage. Advanced NSCLC is usually treated with platinum-based doublet chemotherapy, with inevitable subsequent relapse.

In NSCLC, numerous molecular alterations have been recently reported and defined as driver oncogenes following their role in transforming and maintaining cancer cells in preclinical models, such as epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS), v-Raf murine sarcoma viral oncogene homolog B (BRAF), MNNG HOS transforming gene (MET) and phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PI3KCA) mutations, anaplastic lymphoma kinase (ALK), v-ros avian UR2 sarcoma virus oncogene homolog 1 (ROS1) and rearranged during transfection (RET) chromosomal rearrangements, and PI3KCA, MET, and HER2 amplifications. Most molecular aberrations seem to occur mainly in adenocarcinoma and are more frequently encountered in never smokers. These mutations offer promising new therapeutic approaches, and the use of specific targeted agents has changed the landscape of lung cancer treatment. Agents targeting the abnormal activity of EGFR and ALK kinases have been validated as first-line treatment for advanced NSCLC harboring theses molecular alterations, with a better overall response rate (ORR) and progression-free survival (PFS) compared with standard chemotherapy.

**BRAF Mutations**

The rat sarcoma (RAS)–rapidly accelerated fibrosarcoma (RAF)–mitogen-activated protein/extracellular signal-regulated kinase kinase (MEK)–extracellular signal-regulated kinase (ERK) mitogen-activated protein kinase pathway is one of the most important canonical cancer signaling pathways, mediating cellular responses to growth signals essential for cell proliferation and survival (Fig. 1). Its role in carcinogenesis was initially proposed based on its frequent dysregulation in human cancer. BRAF is a member of the serine/threonine kinase RAF family (including the isoforms v-Raf murine sarcoma viral oncogene homolog A [ARAF], BRAF, v-Raf murine sarcoma viral oncogene homolog C [CRAF]) that is regulated by binding to RAS and directly activating MEK1/2, which can further phosphorylate ERK1/2. RAS and BRAF oncogenic mutations

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Disclosure: No financial support was provided. The authors declare no conflict of interest. No writing assistance was utilized in the production of this manuscript.

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DOI: 10.1097/JTO.0000000000000644

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ISSN: 1556-0864/15/1010-1396
BRAF Alterations as Therapeutic Targets in NSCLC

are usually mutually exclusive events. 5,10,19 BRAF is mutated in 8% of all human cancers, predominately in hairy cell leukemia (100%), melanoma (50%), papillary thyroid carcinoma (45%), colorectal (10%), and rarely in ovarian and lung cancer.5,10,19 Almost all nonsynonymous activating and nonactivating BRAF mutations have been identified in exon 11 and exon 15.19-21 A T1799 point mutation in exon 15 of the BRAF gene, resulting in a valine to glutamate substitution at codon 600 (V600E) affecting the kinase domain of the BRAF protein, is the most common oncogenic driver mutation in melanoma (90%).19,22

The BRAF V600E mutation results in constitutive activation of its serine/threonine kinase, with a high dependency on downstream MEK signaling, and represents an actionable component of this pathway.23,24 BRAF inhibitors have been
extensively studied in melanoma, where vemurafenib and dabrafenib have been approved (in 2011 and 2013, respectively) as single agents for the treatment of patients with advanced melanoma with either a BRAF V600E or V600K mutation.30 Vemurafenib and dabrafenib are type I BRAF serine/threonine kinase inhibitors with selectivity for mutant BRAF V600E, in contrast to type II B-raf inhibitors, which preferentially bind the active site of the serine/threonine kinase domain of BRAF, which is constitutively activated in V600E mutants, with a half maximum inhibitory concentration (IC50) of 31 nM for vemurafenib and 0.65 nM for dabrafenib. The MEK inhibitor trametinib has also been approved (in 2013) as monotherapy for patients with advanced melanoma with either a BRAF V600E or V600K mutation.30

Trametinib is a MEK1/2 inhibitor with a favorable pharmacokinetic profile and a long circulating half-life. The drug inhibits MEK1/2 kinase activity and prevents RAF-dependent MEK phosphorylation.18,19 Recently, the combination of dabrafenib and trametinib has shown superior efficacy compared with BRAF inhibitor monotherapy in BRAF V600E-mutated or V600K-mutated advanced melanomas,32–35 hence becoming the new standard therapy for this indication.

**BRAF Mutations in Lung Cancer**

BRAF mutations are detected in approximately 2% to 4% of lung cancer, hence occurring at a lower frequency than EGFR mutations (10–15%) and probably in a slightly smaller subpopulation than ALK rearrangements (3–5%). These mutations have been predominantly diagnosed in the adenocarcinoma histological subtype, without obvious ethnicity or gender predominance.5,19 Preclinical data in mice suggested a potential oncogenic role of BRAF mutations in the development of lung adenocarcinoma.56 In contrast to melanoma where V600 mutations represent the vast majority of encountered BRAF mutations, V600E mutations represent only about half of BRAF mutations detected in NSCLC. Although V600E mutations are related to an elevated basal kinase activity compared with wild-type BRAF, non-V600E BRAF mutations occur often in the phosphate-binding loop (P-loop), which is the adenosine triphosphate (ATP) binding site.19

### TABLE 1. Clinical Features and Outcome of BRAF-Mutated NSCLC Patients

<table>
<thead>
<tr>
<th>First author</th>
<th>Paik10</th>
<th>Marchetti17</th>
<th>Ilie38</th>
<th>Cardarella39</th>
<th>Luk21</th>
<th>Litvak40</th>
<th>Brustugun41</th>
<th>Villaruz24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td>United States</td>
<td>Italy</td>
<td>France</td>
<td>United States</td>
<td>Australia</td>
<td>United States</td>
<td>Norway</td>
<td>United States</td>
</tr>
<tr>
<td>Patients (n)</td>
<td>697</td>
<td>1046</td>
<td>450</td>
<td>883</td>
<td>273</td>
<td>63</td>
<td>979</td>
<td>951</td>
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<tr>
<td>BRAF (n)</td>
<td>18 (2.6%)</td>
<td>37 (3.5%)</td>
<td>40 (8.9%)</td>
<td>36 (4.1%)</td>
<td>7 (2.6%)</td>
<td>63 (NA)</td>
<td>17 (1.7%)</td>
<td>21 (2.2%)</td>
</tr>
<tr>
<td>V600E (%)</td>
<td>50</td>
<td>57</td>
<td>52</td>
<td>50</td>
<td>57</td>
<td>57</td>
<td>NA (100)</td>
<td>81</td>
</tr>
</tbody>
</table>

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*The clinical features of one patient with non-V600E-mutated squamous cell carcinoma were not reported by Marchetti et al17 and were not taken into account in this table.

1Paik et al10 defined early stage as I to IIIA and advanced stage as IIIB to IV.

2The staging of one patient with BRAF V600E mutant was not reported by Villaruz et al24 and was not taken into account in this table.

3Survival outcome and comparison between studies have to be taken with precaution, as the analyses were conducted over small numbers and different tumor stages.

4OS was calculated for advanced stage BRAF mutants versus other driver mutations (EGFR, KRAS, and ALK).

5OS was compared for early and advanced BRAF mutants versus KRAS or EGFR mutations.

6OS was compared between BRAF mutants and other driver mutants (EGFR, KRAS, ALK) or wild-type.

7Not statistically significant.

8Better OS was found with advanced IIIB to IV stage BRAF V600E mutants, but OS was the same in early I to IIIA stage between V600E and non-V600E mutants.

BRAF, v-Raf murine sarcoma viral oncogene homolog B; NSCLC, non–small-cell lung cancer; NA, not applicable; V600E, valine to glutamate substitution at codon 600; OS, overall survival; wt, wild-type; EGFR, epidermal growth factor receptor; KRAS, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; ALK, anaplastic lymphoma kinase.
The biological and prognostic impact of *BRAF* mutations in NSCLC have been reported in several retrospective studies, all limited by the small patient numbers (Table 1). The prognostic impact of *V600E* and non-*V600E* mutations remain contradictory in the reported series available. Paik et al performed an institutional analysis at Memorial Sloan-Kettering Cancer Center on 697 consecutive early-stage and late-stage lung adenocarcinoma. *BRAF* mutations occurred in 3% of patients, and the mutations identified were *V600E* (50%), G469A, and D594G. All patients were current or former smokers, and there was no difference in overall survival (OS) for *BRAF*-mutated patients when compared with other *EGFR*-mutated, *ALK*-mutated, or *KRAS*-mutated subpopulations.

Marchetti et al reported the results of a retrospective series of 1046 surgically resected NSCLC (squamous and nonsquamous cell) patients. *BRAF* mutations were found in 3.5% of the tumors and in 4.9% of lung adenocarcinoma. The *V600E* mutation occurred in 2.8% of adenocarcinoma, more often among never-smokers, females, and aggressive histological types (micropapillary) and represented 58% of all *BRAF* mutations documented. Patients with the *BRAF V600E* mutation had shorter disease-free survival (DFS) and OS compared with wild-type and non-*V600E* mutations. In contrast, non-*V600E* mutations were found in current or former smokers. There was no difference in disease-free survival or OS observed in patients with or without non-*V600E* mutations. In this analysis, all *BRAF*-mutated tumors were found to be *KRAS* negative. Lu et al conducted a mutation analysis for *BRAF, EGFR*, and *KRAS* in 273 advanced NSCLC patients and found that *BRAF* mutations occurred in 2.6% of cases. All patients had a smoking history in contrast to the *EGFR*-mutated population, and there was no difference in sex distribution between *BRAF* mutant and wild-type patients. The *V600E* mutation accounted in 58% of patients and was associated with the aggressive micropapillary subtype.

According to Cardarella et al, *BRAF* mutations were identified in 4% of lung adenocarcinoma in a retrospective analysis of 883 patients with NSCLC, half of whom had *V600E* mutations. There were no differences in clinical features between *BRAF*-mutated and wild-type patients. However, the analysis suggested that patients with the *V600E* mutation seem to have shorter PFS after platinum-based chemotherapy. Recently, the Lung Cancer Mutation Consortium reported on a series of 63 patients with *BRAF* mutations in advanced stage adenocarcinoma and found a high incidence of *V600E* mutations (80%). *BRAF* mutations were more likely to occur in current or former smokers with no gender predominance. There was no difference in OS between *BRAF* mutant and wild-type patients.

**Therapy of BRAF Mutant NSCLC**

In vitro preclinical models of NSCLC demonstrated that both vemurafenib and trametinib were effective as single agents in *BRAF V600E* mutant cells. Moreover, trametinib was also effective in non-*V600E* mutants. The combination of vemurafenib and trametinib increased tumor cell death, suggesting that the combination should be more effective. Two other MEK inhibitors (PD0325901 and CI-1040) have also shown activity in in vitro and in vivo preclinical models of NSCLC with *BRAF V600E* or non-*V600E* mutations.

In patients with NSCLC harboring the *BRAF V600E* mutation, partial responses (PR) or complete responses (CR) have been reported for vemurafenib and dabrafenib mono-therapies. However, the responses were not durable. Sorafenib has also been reported to be active in patients with *BRAF* mutant NSCLC. An update from the European EURAF cohort study was presented at the European Lung Cancer Conference 2015. This retrospective multicenter study collected data from patients with advanced NSCLC with *BRAF* mutations, who were treated with at least one *BRAF* inhibitor outside of a dedicated clinical trial. Out of 35 patients, all with adenocarcinoma, 83% had *BRAF V600E* mutations, and 17% had non-*V600E* mutations (such as G466V, G469A, G469L, G596V, V600K, and K601E). Seventy-four percent patients received vemurafenib, 23% dabrafenib, and 3% sorafenib. Most patients received one line of *BRAF* inhibitors, whereas 11% patients received two lines of *BRAF* inhibitors. Although most *BRAF* inhibitors (86%) were used after at least one line of chemotherapy, five patients received *BRAF* inhibitors as first line, among who three achieved a PR. ORR was 53%, with 85% disease control rate (DCR), including 6% CR, 47% PR, and 32% stable disease. The planned subgroup analysis of *BRAF* V600E patients receiving vemurafenib showed 54% ORR and 96% DCR. PFS with first-line therapy (including chemotherapy) was 9.3 months for V600E and 1.5 months for non-V600E, and OS was 25.2 and 11.8 months, respectively. Overall, PFS and OS using a *BRAF* inhibitor for V600E mutants were 5 and 10.8 months, respectively. The duration of *BRAF* therapy was 4.3 months, ranging from 0.5 to 41 months, with some patients having durable responses. Most patients with non-*V600E* mutations did not respond to *BRAF* inhibitors and had a significantly poorer outcome, although CR was observed with one *BRAF G596V*-mutated NSCLC patient treated with vemurafenib. The mechanism of non-*V600E* *BRAF*-mutated NSCLC primary resistance to *BRAF* inhibitors is not fully understood. Three-dimensional structural modeling of *BRAF G469L* suggested that it induces a conformational change impairing the binding of vemurafenib and dabrafenib.

**Prospective Studies**

There are very few completed or ongoing prospective clinical trials in *BRAF*-mutated NSCLC, undoubtedly related to the rarity of these alterations and subsequent difficulty in enrolling and randomizing these patients. The multicenter VE-BASKET (NCT01524978) phase II study is assessing vemurafenib in *BRAF V600*-mutated nonmelanoma solid tumors, including NSCLC. Out of 19 patients with NSCLC, 42% had unconfirmed PR and 42% had stable disease. The study is still recruiting. AcSé (NCT02304809) is a French phase II study evaluating vemurafenib monotherapy in patients with *BRAF V600*-mutated nonmelanoma solid tumors, including NSCLC. Results are pending.

The interim results of the BRF113928 (NCT01336634) prospective study was recently presented at the 2015 American Society of Clinical Oncology annual meeting. This multicenter, single-arm, two-stage, open-label phase II study assessed the safety and efficacy of dabrafenib and trametinib in patients with stage IV NSCLC with *BRAF V600E* mutation,
after failure of at least one line of chemotherapy. The first stage of the study evaluated the safety of dabrafenib as monotherapy. In 78 patients who received at least one prior line of treatment, ORR was 32%, DCR for more than 3 months was 56%, duration of response was 11.8 months, and 48% of responders had progressive disease. Among the six patients who received dabrafenib as first-line treatment, three achieved a PR. The most common adverse events (AEs) were similar to dabrafenib treatment in melanoma. Serious AEs occurred in 45%, with one death from intracranial hemorrhage. The second stage of the study evaluated the safety and efficacy of dabrafenib combined with trametinib. Out of 33 treated patients, 82% remained on therapy at the time of the interim analysis, 12% had progressive disease, and 6% stopped because of AEs. Out of 24 evaluable patients, ORR was 63%, and DCR for more than 3 months was 88%, suggesting a superior antitumor activity than dabrafenib monotherapy. Toxicities were manageable and similar to those seen in previous studies in melanoma. Since the study passed the futility interim analyses, recruitment is ongoing. A third cohort assessing the combination treatment in previously untreated BRAF V600E NSCLC is currently recruiting.

A novel BRAF inhibitor LGX818 is currently being evaluated as monotherapy in an open-label, multicenter, single-arm phase II study in BRAF V600-mutated advanced NSCLC (NCT02109653). LGX818 is also being evaluated either in combination with the MEK inhibitor MEK162 or as a triplet combination with MEK162 and the cyclin-dependent kinase inhibitor LEE011 in an open-label, multicenter, phase Ib/II study in BRAF-mutated advanced solid tumors (NCT01543698). Other interesting ongoing studies are the phase Ib/II studies assessing the phosphatidylinositol 3-kinase (PI3K) inhibitor BKM120 either in combination with trametinib (NCT01155453) or the MEK inhibitor MEK162 (NCT01363232) in selected advanced solid tumors, including BRAF-mutated NSCLC. The MEK inhibitor selumetinib is also being assessed in a phase II study in nonmelanoma tumors with BRAF mutations (NCT00888134).

**DISCUSSION**

BRAF mutations represent rare driver alterations found in lung adenocarcinoma. Beyond this histological subtype, there is to date no clear clinical or pathological parameter that correlates with a higher prevalence of BRAF mutations. These mutations have been reported in heavy smokers, regardless of ethnicity and gender. The prognostic impact of BRAF mutations remains unclear to date, limited by the small numbers studied, with some series suggesting a worse outcome in this patient population.

Single-agent BRAF inhibitor therapy demonstrates activity in NSCLC; however, this activity is inferior to previous observations using ALK or EGFR tyrosine kinase inhibitors (TKIs) in related oncogene-addicted NSCLC. It appears that the type of BRAF mutation observed is predictive of response to BRAF inhibitor therapy, with V600E mutations presenting with higher response rates and PFS. However, the numbers of non-V600E mutations treated prospectively is still very low, and no conclusion can be drawn yet. Furthermore, some specific non-600E mutations might confer sensitivity to BRAF inhibitors, such as G596V mutation. Of interest, a complete response was achieved with the TKI dasatinib in a unique case of NSCLC harboring BRAF Y472C. Further characterization of non-V600E mutations is required.

Importantly, all patients treated with BRAF inhibitors will eventually demonstrate tumor progression. Resistance mechanisms to BRAF inhibitors are being thoroughly characterized in melanoma and consist of elevated expression of the kinases CRAF, COT or mutant BRAF, activating mutations in neuroblastoma RAS viral (v-ras) oncogene homolog (NRAS), MEK1 or Ak strain AKTI, aberrant splicing of BRAF, activation of PI3K through the loss of phosphatase and tensin homolog (PTEN), and persistent activation of receptor tyrosine kinases, including platelet-derived growth factor receptor β (PDGFRβ), insulin-like growth factor 1 receptor (IGF-1R), and EGFR. However, resistance mechanisms to BRAF inhibitors in NSCLC have not been characterized yet. In a single case of BRAF V600E-mutated NSCLC treated with dabrafenib, molecular profiling revealed three new acquired mutations in KRAS, TP53, and CDKN2A. This highlights the need to conduct serial biopsies and molecular profiling at baseline and at progression to gain insight into BRAF inhibitor resistance mechanisms.

A combination of BRAF and MEK inhibitors may delay the time to resistance/progression, similar to the situation in preclinical models and in melanoma. The dabrafenib and trametinib combination in BRAF V600E-mutated NSCLC demonstrated very promising response rates that surpass those of dabrafenib monotherapy, with safety profiles similar to those found in melanoma. Results from the combination of LGX818 and MEK162 are awaited.

**Future Strategies for BRAF-Mutated NSCLC**

BRAF mutations have been identified in a variety of cancers, including NSCLC. Identifying the mechanisms of resistance to BRAF inhibitors in BRAF-mutated NSCLC will undoubtedly help in refining treatment strategies in the future. Moreover, it will guide strategies for front-line RAF targeted treatment or treatment at resistance. The role of dual BRAF/MEK inhibition could also be better defined. Some mechanisms of resistance reported in melanoma may be relevant in NSCLC. Recently, mechanisms of resistance to combined BRAF/MEK inhibition in melanoma have also been proposed. These comprise BRAF alterations, BRAF amplifications, MEK mutations, PI3K–AKT–mammalian target of rapamycin (mTOR) pathway alterations, PTEN loss, cell cycle protein alteration, and NRAS mutations. One strategy to circumvent resistance to BRAF/MEK inhibitors is to combine other pathway inhibitors, such as PI3K–AKT–mTOR inhibitors, ERK inhibitors, or CDK4/CDK6 inhibitors. Tumor biopsies and analysis at progression is going to be necessary for full elucidation of resistance mechanisms. This will allow for the development of rational, evidence-based strategies for the next generation of clinical trials.

Non-V600E mutations should be better characterized in NSCLC to find appropriate agents for therapy. A better description of the genomic landscape of such tumors would be of great interest. Interestingly, some non-V600E mutations seem to have variable degrees of kinase activity and might even confer resistance to BRAF inhibitors but are possibly sensitive to MEK inhibitors through transactivation of other mechanisms.

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*Journal of Thoracic Oncology® • Volume 10, Number 10, October 2015*
CRAF.23 Thus, combinations of BRAF with MEK inhibitors should also be a potential option in this scenario.

Recently, with the emergence of immunotherapy and the recently reported striking benefit of checkpoint inhibitors in unselected patients with NSCLC in second-line therapy when compared with chemotherapy,72–78 more treatments can be offered to patients, and the opportunity for drug combinations as well as the sequence of different compounds become a field of debate. Obviously, the right sequence of treatment—including chemotherapy, targeted agents and immunotherapy—should be rigorously tested in clinical trials.

Combining BRAF and/or MEK inhibitors and immunotherapy is tempting, and clinical trials testing these combinations are ongoing in melanoma but not in NSCLC yet. In favor of this strategy, recent studies demonstrated that high loads of mutations and tumor heterogeneity can increase the chance of benefitting from anti-CTLA-4 or programmed cell death protein 1 (PD-1) immunotherapy by generating tumor neoepitopes that are used as neoantigens and bind to major histocompatibility complex (MHC) class I molecules with great affinity.77–80 A higher mutational load has been reported in patients with a smoking history,81 BRAF mutations are often found in smokers. In addition, there are several small series suggesting tolerability and promising activity of combining TKIs and checkpoint inhibitors in NSCLC, suggesting that the combination of BRAF/MEK inhibitors with immunotherapy merits further research. As a direct consequence, BRAF-mutated patients should not be excluded from immunotherapy treatment strategies.

CONCLUSION
The landscape of NSCLC treatment has dramatically changed since the emergence of targeted agents against actionable driver mutations, among which BRAF mutations belong. With immunotherapy soon becoming standard treatment after platinum-based chemotherapy, the complexity and diversity of treatment options is broadening. Finding the right personalized biology-driven treatment for each patient at baseline and at recurrence is the quest for the next years to come.

There is a strong need to better characterize resistance mechanisms and validate predictive and prognostic biomarkers that will help treatment decision. To this end, molecular profiling of tumors at diagnosis and at subsequent relapse is crucial. The ability to molecularly characterize tumors through the use of circulating tumor cells or tumor DNA (so called liquid biopsies) will be a significant advance. It appears that this approach may indeed be feasible.52,83

Although such questions will always remain restricted to relatively small clinical trials, an international collaborative effort will be needed to accurately define standards of care in BRAF-mutated NSCLC and allow for the registration of new treatment options for this tiny patient population.

REFERENCES


