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### Authors

Drilon, Alexander
Duruisseaux, Michael
Han, Ji-Youn
et al.



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# Clinicopathologic Features and Response to Therapy of *NRG1* Fusion–Driven Lung Cancers: The eNRGy1 Global Multicenter Registry

Alexander Drilon, MD[1]; Michael Duruisseaux, MD[2,3,4]; Ji-Youn Han, MD, PhD[5]; Masaoki Ito, MD, PhD[6,7,8]; Christina Falcon, MPH[1]; Soo-Ryum Yang, MD[1]; Yonina R. Murciano-Goroff, MD, DPhil[9]; Haiquan Chen, MD, PhD[10,11]; Morihito Okada, PhD[8]; Miguel Angel Molina, PhD[12]; Marie Wislez, MD, PhD[13,14]; Philippe Brun, MD[15]; Clarisse Dupont, MD[2]; Eva Branden, PhD[16,17]; Giulio Rossi, MD, PhD[18,19]; Alexa Schrock, PhD[20]; Siraj Ali, MD, PhD[20]; Valérie Gounant, MD[21]; Fanny Magne, MD[22]; Torsten Gerriet Blum, MD[23]; Alison M. Schram, MD[9]; Isabelle Monnet, MD[24]; Jin-Yuan Shih, MD, PhD[25]; Joshua Sabari, MD[26]; Maurice Pérol, MD[27]; Viola W. Zhu, MD[28]; Misako Nagasaka, MD[29,30]; Robert Doebele, MD, PhD[31]; D. Ross Camidge, MD, PhD[31]; Maria Arcila, MD[1]; Sai-Hong Ignatius Ou, MD, PhD[32]; Denis Moro-Sibilot, MD[33]; Rafael Rosell, MD, PhD[34]; Lucia Anna Muscarella, PhD[35]; Stephen V. Liu, MD[36]; and Jacques Cadranel, MD[37]

abstract

**PURPOSE** Although *NRG1* fusions are oncogenic drivers across multiple tumor types including lung cancers, these are difficult to study because of their rarity. The global eNRGy1 registry was thus established to characterize *NRG1* fusion–positive lung cancers in the largest and most diverse series to date.

**METHODS** From June 2018 to February 2020, a consortium of 22 centers from nine countries in Europe, Asia, and the United States contributed data from patients with pathologically confirmed *NRG1* fusion–positive lung cancers. Profiling included DNA-based and/or RNA-based next-generation sequencing and fluorescence in situ hybridization. Anonymized clinical, pathologic, molecular, and response (RECIST v1.1) data were centrally curated and analyzed.

**RESULTS** Although the typified never smoking (57%), mucinous adenocarcinoma (57%), and nonmetastatic (71%) phenotype predominated in 110 patients with *NRG1* fusion–positive lung cancer, further diversity, including in smoking history (43%) and histology (43% nonmucinous and 6% nonadenocarcinoma), was elucidated. RNA-based testing identified most fusions (74%). Molecularly, six (of 18) novel 5′ partners, 20 unique epidermal growth factor domain–inclusive chimeric events, and heterogeneous 5′/3′ breakpoints were found. Platinum-doublet and taxane-based (post–platinum-doublet) chemotherapy achieved low objective response rates (ORRs 13% and 14%, respectively) and modest progression-free survival medians (PFS 5.8 and 4.0 months, respectively). Consistent with a low programmed death ligand-1 expressing (28%) and low tumor mutational burden (median: 0.9 mutations/megabase) immunophenotype, the activity of chemoimmunotherapy and single-agent immunotherapy was poor (ORR 0%/PFS 3.3 months and ORR 20%/PFS 3.6 months, respectively). Afatinib achieved an ORR of 25%, not contingent on fusion type, and a 2.8-month median PFS.

**CONCLUSION** *NRG1* fusion–positive lung cancers were molecularly, pathologically, and clinically more heterogeneous than previously recognized. The activity of cytotoxic, immune, and targeted therapies was disappointing. Further research examining *NRG1*-rearranged tumor biology is needed to develop new therapeutic strategies.

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ASSOCIATED CONTENT

**Data Supplement**

Author affiliations and support information (if applicable) appear at the end of this article.

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## INTRODUCTION

Gene fusions are enriched in non–small-cell lung cancers (NSCLCs). Many of these fusions encode chimeric oncoproteins that drive cancer growth.[1-4] Activating fusions involving *ALK*,[5-7] *ROS1*,[8-11] *RET*,[12-15] *NTRK1*, *NTRK2*, or *NTRK3*[2,16,17] result in constitutive kinase domain activation that drives downstream pathway signaling, promoting lung cancer cell proliferation and survival. Most importantly, the identification of these fusions matches patients to highly active targeted therapies that are approved by one or more regulatory agencies around the world.[2-4]

*NRG1* fusions are a relatively recent addition to this list of fusion oncogenes.[18-21] Structurally, these alterations are distinct from the aforementioned fusions. The transmembrane chimeric oncoprotein contains the epidermal growth factor or epidermal growth factor–like binding domain of NRG1, a known ligand of ERBB3. Binding of the oncoprotein to ERBB3 results in the formation of heterodimers between ERBB3 and

## CONTEXT

**Key Objective**

The goals of the eNRGy1 global multicenter registry are to characterize the features of *NRG1* fusion–positive lung cancers and elucidate the clinical activity of systemic therapy in a centrally curated real-world database of patients with these rare cancers.

**Knowledge Generated**

*NRG1* fusion–positive lung cancers are pathologically, clinically, and molecularly more diverse than previously recognized. Many fusions are first detected by RNA-based sequencing. A variety of unique chimeric events are identified. Most tumors are characterized by no or low programmed death ligand-1 expression and low tumor mutational burden. The activity of a variety of cytotoxic, immunotherapy, and targeted therapy regimens is modest at best.

**Relevance**

Comprehensive sequencing to identify *NRG1* fusions should capture molecularly heterogeneous events and not be biased toward particular clinical or pathologic features. To develop novel therapeutic strategies, stakeholders should prioritize research into the underexplored biology of *NRG1* fusion–positive tumors and the development of rationally designed drugs.

other ERBB family members, thereby activating oncogenic signaling and cancer growth. Of these heterodimers, ERBB3-ERBB2 is the most transforming. Therapeutic targeting of these fusions has thus centered on the inhibition of ERBB3 and/or ERBB2.[22-29] For example, individual case reports or small series have noted clinical benefit with the pan-ERBB1/2/4 tyrosine kinase inhibitor afatinib in selected patients.[22,23,25,26,30]

Although *NRG1* fusions were first discovered in lung cancers in 2014,[19] the clinical, pathologic, and molecular features of these cancers are yet to be comprehensively characterized in a large series.[23,31] In addition, the activity of many systemic therapies in this molecularly enriched cohort of patients has not been well-described. To address this unmet need, we formed the eNRGy1 global multicenter consortium of thoracic oncology investigators to contribute data on patients with *NRG1* fusion–positive lung cancers to a central registry.

## METHODS

### eNRGy1 Global Multicenter Registry

Investigators taking part in the consortium were initially identified on the basis of their contributions to existing registries for other molecularly defined lung cancer subtypes, including those with *RET* rearrangements,[14] *BRAF* mutations,[32] *HER2* mutations,[33,34] and *ROS1* rearrangements.[35] All investigators were certified in good clinical practice and obtained ethics review board approval through their individual institutions.

### Eligible Patients

Patients were considered eligible for registry inclusion if they had a pathologically confirmed diagnosis of lung cancer with an *NRG1* fusion as determined by testing in an accredited laboratory. Acceptable testing methods for *NRG1* fusion detection included fluorescence in situ hybridization using the Agilent, Clinisciences, or ZytoVision assays (fusion-positive tumors were defined as those with split signals or isolated red [3′] signals in ≥ 15% of enumerated tumor cells)[36]; DNA-based and/or RNA-based next-generation sequencing (NGS) using MSK-IMPACT, FoundationOne, Caris NGS, ION Ampliseq, Oncomine, StrataNGS, or Archer; reverse transcription-polymerase chain reaction (PCR); or through detection of imbalanced gene expression via nCounter gene fusion panels (NanoString Technologies, Seattle, WA).

### Clinicopathologic Data

Investigators were asked to record data on patient demographics (including sex, age at diagnosis, smoking habits, and ethnicity) and tumor pathologic features (including stage, histology as determined by a local pathologist, and *NRG1* fusion partner). Treatment history, including the date of diagnosis, treatments received, dates of progression, and survival status were documented. For survival analysis, patients were followed through February 2020. Best overall response to treatment was determined according to RECIST version 1.1, which was assessed locally at each institution.

### Immunophenotype

Programmed death ligand-1 (PD-L1) expression in tumor cells was determined by immunohistochemistry.[37] Because of the variability in measures of tumor mutational burden (TMB) using different sequencing assays,[38-40] TMB was only collected for those patients whose tissue underwent sequencing using a single NGS assay, MSK-IMPACT. MSK-IMPACT is a targeted, hybrid capture-based NGS DNA assay that covers up to 468 cancer-related genes.[41] This assay has been extensively validated for the assessment of TMB.[40,42,43] The TMB of *NRG1* fusion–positive

tumors was compared with that recorded for all other lung cancers that underwent sequencing using MSK-IMPACT.

### Data Collection and Analysis

Investigators from the global consortium submitted anonymized data to a database maintained at one institution between June 2018 and February 2020. Categorical variables were compared using Fisher's exact tests. Continuous variables were compared using Mann-Whitney testing. Progression-free survival (PFS) was assessed from therapy initiation until radiologic progression (by RECIST v1.1) or death. Overall survival (OS) was assessed from the date of initial diagnosis through death. Survival analyses were carried out according to the Kaplan-Meier method, with surviving patients censored at the date of last follow-up.

Statistical analyses were performed using GraphPad Prism version 8.4.2 (San Diego) or R version 3.4.0 (R Project for Statistical Computing, Vienna, Austria). STATA (version 16, College Station, TX) was used to calculate confidence intervals for Kaplan-Meier curves. The results were considered statistically significant if they fell below the $P = .05$ threshold.

## RESULTS

### Clinicopathologic Features

Data from 110 patients with *NRG1* fusion–positive lung cancers were contributed by a total of 22 different centers from nine countries in Europe, Asia, and the United States. Demographics are summarized in Table 1. The median age was 64 years. The majority of patients were either Asian (52%) or White (46%). Most patients (57%) were never smokers. In patients with a prior or current history of smoking (n = 36), the median pack-year history was 37.

At the time of diagnosis, most (71%, n = 58/82) patients had nonmetastatic (stages I-III) disease. In patients with metastatic disease diagnosed at any time during their disease course (n = 44), the most common sites of metastasis were the lung (71%, n = 31/44), bone (34%, n = 15/44), and lymph nodes (23%, n = 10/44). Intrathoracic metastases (involving the mediastinum [2%, n = 1/44], the pleura [16%, n = 7/44], the contralateral lung [71%, n = 31/44], and lymph nodes [23%, n = 10/44]) were frequent (77%, n = 34/44). Extrathoracic metastases were found in 43% (n = 19/44) of patients. The frequency of metastases and their sites are shown in Figure 1A and the Data Supplement (online only). Adenocarcinoma was the most common histology, found in 94% (n = 103/110) of patients. In adenocarcinomas, invasive mucinous adenocarcinoma (IMA) was the most frequent (57%) subtype as shown in Figure 1B.

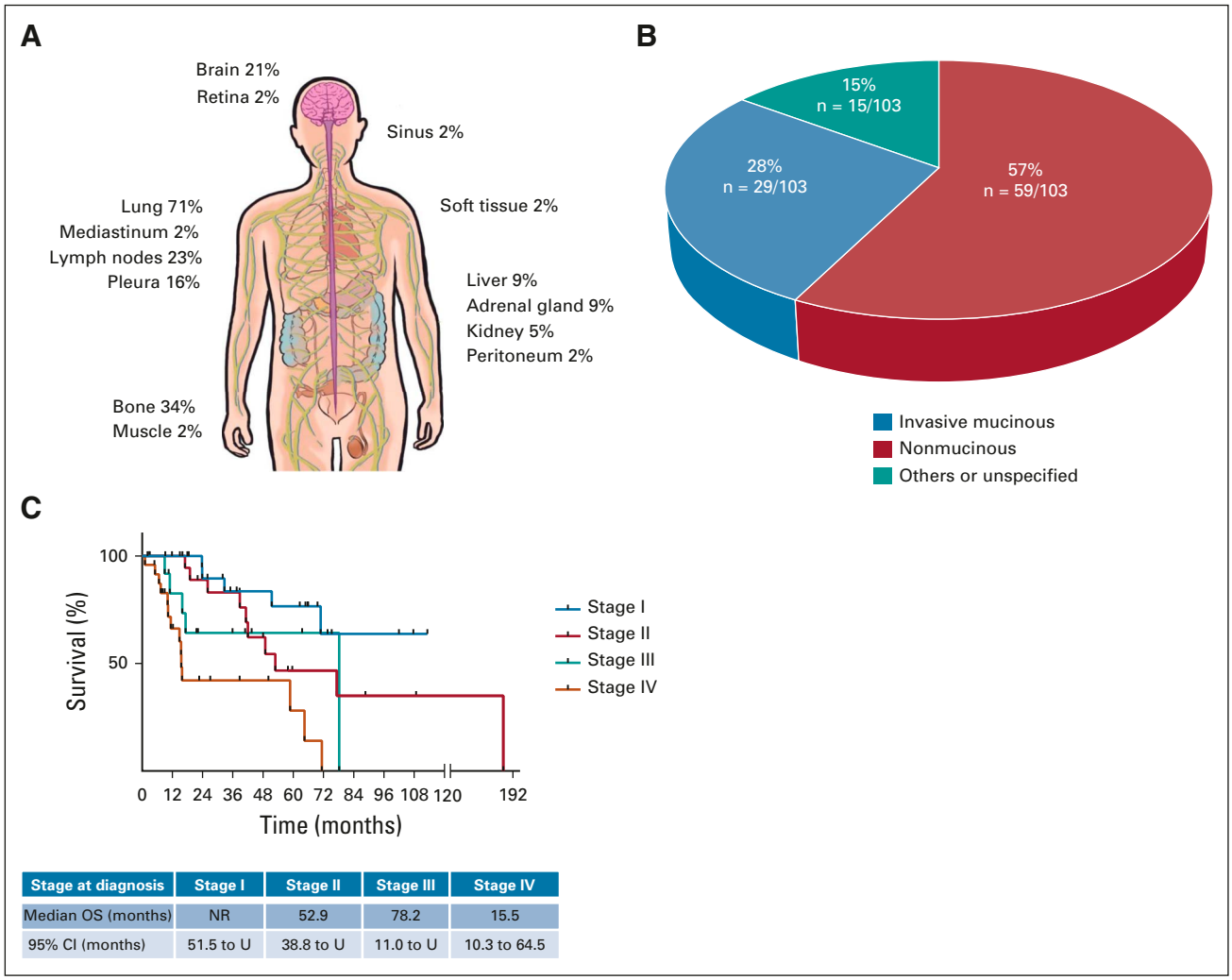
Kaplan-Meier plots of OS are shown in Figure 1C and the Data Supplement by stage at diagnosis. The median OS by stage was not reached (95% CI, 51.5 to undefined) for stage I (n = 26) and was 52.9 months (95% CI, 38.8 to

**TABLE 1.** Clinicopathologic Characteristics

| Characteristic | No. (%), (N = 110) |
|---|---|
| Sex | |
| Male | 42 (41) |
| Female | 62 (59) |
| Median age (range), years | 64 (29-88) |
| Ethnicity | |
| Asian | 43 (52) |
| White | 38 (46) |
| Black | 2 (2) |
| Smoking status | |
| Never | 48 (57) |
| Former | 25 (30) |
| Current | 11 (13) |
| Median pack-years (range) | 37 (1-135) |
| Stage at diagnosis | |
| I | 26 (32) |
| II | 19 (23) |
| III | 13 (16) |
| IV | 24 (29) |
| Histology | |
| Adenocarcinoma | 103 (94) |
| Invasive mucinous | 59 (57) |
| Invasive nonmucinous | 29 (28) |
| Others or unspecified | 15 (15) |
| Adenosquamous | 1 (< 1) |
| Squamous | 4 (4) |
| Large cell neuroendocrine | 1 (< 1) |
| NSCLC (NOS) | 1 (< 1) |
| Geographic distribution | |
| United States | 47 (43) |
| South Korea | 21 (19) |
| France | 14 (13) |
| Italy | 12 (11) |
| Japan | 7 (6) |
| China | 6 (5) |
| Germany | 1 (< 1) |
| Sweden | 1 (< 1) |
| Taiwan | 1 (< 1) |

NOTE. The percent frequency of individual features is based on the denominator of patients for whom information is known: sex (n = 104), median age (n = 104), ethnicity (n = 83), smoking status (n = 84), median pack-year (n = 84), stage at diagnosis (n = 82), and histology (n = 110). The frequency of missing data on individual features is as follows: sex, n = 6 (5%); median age, n = 6 (5%); ethnicity, n = 27 (25%); smoking status, n = 26 (24%); median pack-year, n = 26 (24%); stage at diagnosis, n = 28 (25%); and histology, n = 0 (0%).

Abbreviations: NOS, not otherwise specified; NSCLC, non–small-cell lung cancer.




| Stage at diagnosis | Stage I | Stage II | Stage III | Stage IV |
|---|---|---|---|---|
| Median OS (months) | NR | 52.9 | 78.2 | 15.5 |
| 95% CI (months) | 51.5 to U | 38.8 to U | 11.0 to U | 10.3 to 64.5 |

**FIG 1.** Clinicopathologic features. (A) The frequency of metastasis to selected anatomic sites is shown for patients with *NRG1* fusion–positive lung cancers. (B) The histologic subtypes of 103 *NRG1* fusion–positive adenocarcinomas are shown. These are divided into invasive mucinous adenocarcinomas, noninvasive mucinous adenocarcinomas, and other subtypes. (C) Kaplan-Meier curves of OS are shown for stage I (blue), stage II (red), stage III (green), and stage IV (orange) disease at diagnosis. The median duration of follow-up was 32 months (range, 1-179 months). NR, not reached; OS, overall survival; U, undefined.

undefined) for stage II (n = 19), 78.2 months (95% CI, 11.0 to undefined) for stage III (n = 13), and 15.5 months (95% CI, 10.3 to 64.5) for stage IV (n = 24).

### Fusion Diagnosis

RNA-based testing was the most common method that identified *NRG1* fusions: 74% were detected by RNA-based assays and 26% were detected by DNA-based assays (Fig 2A). Of the RNA-based assays, *NRG1* fusions were most commonly identified by amplicon-based RNA sequencing using anchored multiplex PCR (62%, n = 50/81) followed by reverse transcription-PCR (27%, n = 22/81) and expression analysis using nCounter (11%, n = 9/81).

Using DNA-based assays, *NRG1* fusions were almost equally detected by NGS (52%, n = 15/29) and fluorescence in situ hybridization (48%, n = 14/29). When detected by NGS, the majority of *NRG1* fusions were detected using hybrid capture-based testing (93%, n = 14/15) compared with amplicon-based testing (7%, n = 1/15).

### Molecular Features

A plot of the various *NRG1* fusions identified is shown in Figure 2B and summarized in the Data Supplement. Upstream gene partners were identified in 92 fusions (84%), and breakpoints in 67 fusions (61%). Eighteen unique upstream gene partners were identified, and 13 with known exonic breakpoints are depicted in Figure 2C. The most common upstream partners were *CD74* (41%) and *SLC3A2* (20%). Less common partners were *SDC4*, *FGFR1*, *ATP1B1*, *CADM1*, *DIP2B*, *F11R*, *FLYWCH1*, *ITGB1*, *KRAS*, *MDK*, *MRPL13*, *PLCG2*, *RBPMS*, *TNC*, *VAMP2*, and *VAPB*.

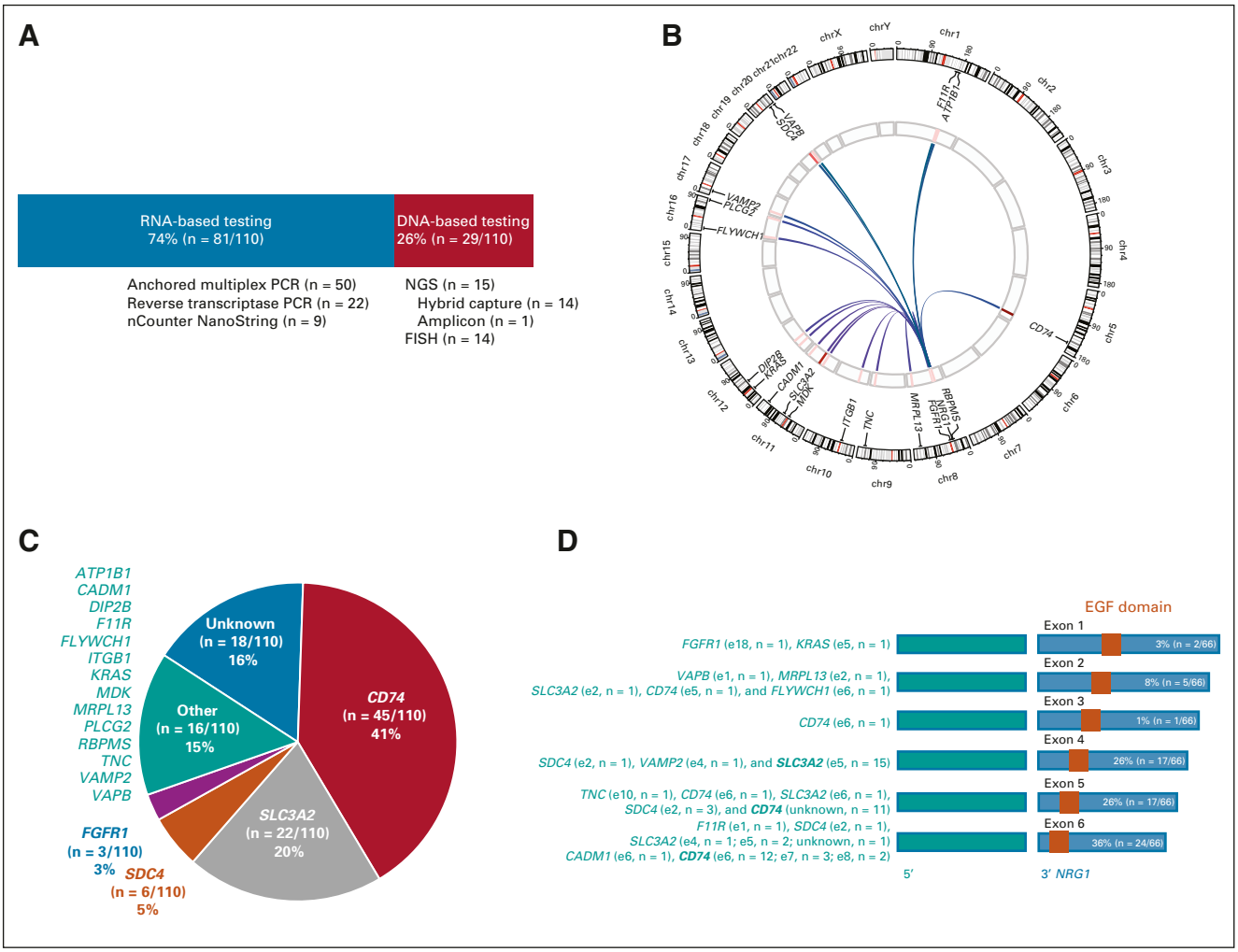



**FIG 2.** Molecular features. (A) The primary assay that identified the *NRG1* fusion in cancers from 110 patients in this registry is divided into RNA-based (blue) and DNA-based (red) assays. Below each corresponding bar, a list and number of the individual assays are shown. (B) A Circos plot of the various *NRG1* fusions detected and their corresponding upstream partners is shown. The intensity of the red bars in the inner circle represents the frequency of each fusion event, with darker bars representing more common fusions and lighter bars representing less common fusions. (C) The frequency of upstream partners is shown. The most common 5′ partners—*CD74*, *SLC3A2*, *SDC4*, and *FGFR1*—are shown individually, whereas less common partners are aggregated into other partners (green). (D) When known, the exon that precedes the 5′ breakpoint is shown in green along with the frequency of each event. Exons and exon numbers are abbreviated as eX (e for exon and X for exon number), and events that occur in more than 10 fusions in aggregate are in boldface. The structure of the corresponding 3′ *NRG1* gene is shown, with the first exon shown after the breakpoint noted above each blue bar. EGF domains are depicted as orange boxes. EGF, epidermal growth factor; FISH, fluorescence in situ hybridization; NGS, next-generation sequencing; PCR, polymerase chain reaction.

The various breakpoints as reported by local molecular testing assays are shown in Figure 2D for 20 unique chimeric events. For *CD74*, the breakpoint occurred most commonly after exon 6, followed by exon 8 and exon 7. For *SLC3A2*, the breakpoint occurred most commonly after exon 5. For *NRG1*, the breakpoint most commonly involved exon 6, followed by exons 4 and 5, followed by exon 2. All *NRG1* fusions included the *EGF* domain that binds ERBB3.

*NRG1* fusions were mutually exclusive with other known oncogenic drivers in the majority of patients (94%, n = 103/110). In the remaining seven patients (Data Supplement), a concurrent driver was identified. Four had hotspot *KRAS* mutations (KRAS G12C, n = 1; KRAS G12V, n = 1; KRAS G12D, n = 2), all of which are drivers known to occur in IMAs. Three had either an *EGFR* mutation (EGFR L858R, n = 2) or an *ALK* fusion (*EML4-ALK* variant 3, n = 1). In three patients (Data Supplement), the concurrent driver was clearly present de novo. Two patients with surgically resected stage IB/IIB *NRG1* fusion–positive IMAs had a concurrent KRAS G12D substitution found at the time of surgery (with no preceding neoadjuvant therapy). One patient had *NRG1* and *ALK* fusions that were both found in the same sample acquired at the diagnosis of metastatic disease before any systemic therapy. This patient

responded to crizotinib for 13 months, followed by ceritinib for 18 months.

### Immunophenotype

Tumor PD-L1 status was known for 46 of the 110 patients (42%) and is shown in Figure 3A. The antibodies used for PD-L1 testing were 22C3 (n = 26), E1L3N (n = 14), and QR1 (n = 4), with testing on two tumors carried out using an unspecified assay. High PD-L1 expression (50% or greater) was rare (4%, n = 2/46). The majority of tumors had either no expression of PD-L1 in 72% (n = 33/46) of tumors or PD-L1 expression of 1%-49% in 24% (n = 11/46) of tumors.

*NRG1* fusions were also characterized by low TMB as shown in Figure 3B. As measured by MSK-IMPACT, the median TMB of *NRG1* fusion–positive lung cancers was 0.9 mutations/megabase (range, 0-2.6; n = 11). This was lower than that in patients with *ALK* (1.8 mutations/megabase, $P = .03$; n = 157), *ROS1* (2.6 mutations/megabase, $P = .0008$; n = 85), *RET* (2.6 mutations/megabase, $P = .0006$; n = 95), and *NTRK1/2/3* (4.9 mutations/megabase, $P = .003$; n = 13) fusion–positive lung cancers. Similarly, the median TMB of *NRG1* fusion–positive was lower ($P < .0001$) than that of 5,380 lung cancers (5.9 mutations/megabase) that did not harbor fusions involving *ALK*, *ROS1*, *RET*, or *NTRK*.

### Chemotherapy and Immunotherapy Activity

The activity of systemic therapy was assessed in patients either diagnosed with or who developed metastatic disease during the course of their disease (Data Supplement). Outcomes are summarized in Table 2. In evaluable patients who received platinum-doublet–based chemotherapy, many of whom received pemetrexed, only 13% (n = 2/15) had a response; the disease control rate was 60% (n = 9/15). The median PFS was 5.8 months (95% CI, 2.2 to 9.8; range, 0.7-12.1 months; Fig 4A and Data Supplement). In patients who received taxane-based chemotherapy in the post–platinum-doublet setting, one response (14%, n = 1/7) was observed and the most common outcome was progressive disease (71%, n = 5/7). The median PFS was 4.0 months (95% CI, 0.8 to 5.3; range, 0.8-5.5 months; Fig 4B).

Consistent with the immunophenotype of these cancers, the activity of single-agent immune checkpoint inhibition was modest (Data Supplement, Figs 4C and 4D). In patients evaluable for response, the most common outcome was progressive disease (60%, n = 3/5). Only one patient had a partial response that lasted more than 11 months. The median PFS was 3.6 months (95% CI, 0.9 to undefined; range, 0.9-11.2 months; Data Supplement). No responses (0%, n = 0/9) were observed in patients treated with chemoimmunotherapy (most of whom received carboplatin, pemetrexed, and pembrolizumab), for whom progressive disease occurred in more than half of patients (56%, n = 5/9). The median PFS was 3.3 months (95% CI, 1.4 to 6.3; range, 1.4-15.2 months; Fig 4D).

### Afatinib Activity

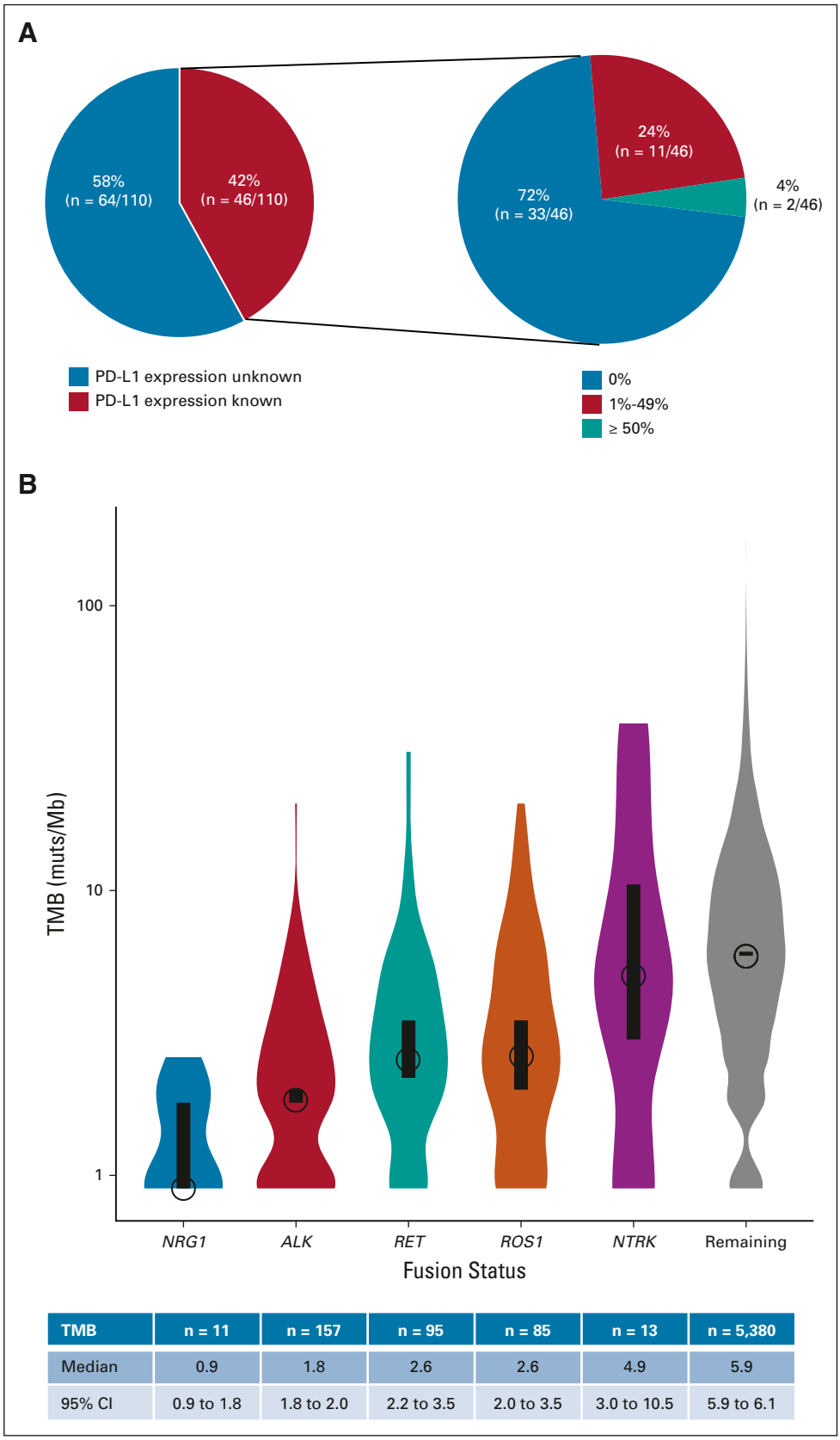
As *NRG1* fusions are dependent on ERBB signaling, several investigators have explored the use of afatinib, a pan-ERBB inhibitor, in patients with these cancers.[22,25,26,30,44] A response was achieved in 25% (n = 5/20, all partial responses) of evaluable patients treated with afatinib (Table 2 and Data Supplement). The fusion partners were known in four of five patients, including *CD74* (n = 2), *SLC3A2* (n = 1), and *SDC4* (n = 1). Stable disease occurred in another 15% (n = 3/20) of patients. The most common response to afatinib was progressive disease, which occurred in 60% (n = 12/20) of patients. The response rate in cancers with *CD74-NRG1* and non-*CD74-NRG1* fusions was 22% (n = 2/9) and 27% (n = 3/11), respectively.

In addition, the duration of clinical benefit with afatinib was limited. The swimmer's plot of afatinib monotherapy is shown in Figure 4E. The median PFS with afatinib was 2.8 months (95% CI, 1.9 to 4.3; range, 0.3-25.3 months; Data Supplement). PFS did not differ for patients with tumors harboring CD74 fusion partners versus other fusion types (Data Supplement). There was no significant difference ($P > .05$) in OS when patients who received afatinib were compared with patients who did not receive afatinib.

## DISCUSSION

This global registry represents the largest series of patients with *NRG1* fusion–positive lung cancers reported to date. As a testament to the utility of multinational consortia such as this one, the number of patients featured here is several fold higher than the number identified through analysis of data from single institutions, large-scale sequencing laboratories, or even The Cancer Genome Atlas.[23,31] Despite the retrospective nature of the study and its inherent limitations such as reporting bias and the lack of prospective sequencing data, complete clinical annotation for every patient, and central radiologic assessment, this underscores the utility of such cooperative endeavors to generate meaningful real-world data, particularly in rare genotype-driven cancers.

Although the data generated here confirm preliminary observations reported in prior smaller series or case reports, including publications from members of this registry,[23,30,36] several new clinicopathologic observations emerged. More than half of patients were initially diagnosed with stage I or II disease, although many subsequently developed metastatic disease. Whereas intrathoracic metastases predominated, consistent with the natural history of many IMAs,[45,46] extrathoracic metastases were observed in more than 40% of patients. Additionally, although *NRG1* fusions were strongly associated with IMAs in prior series,[24,46,47] nonmucinous adenocarcinomas represented more than a quarter of cases. These fusions were also found in non-adenocarcinoma histologies, including squamous cell and large cell neuroendocrine cancers, suggesting that




| TMB | n = 11 | n = 157 | n = 95 | n = 85 | n = 13 | n = 5,380 |
|---|---|---|---|---|---|---|
| Median | 0.9 | 1.8 | 2.6 | 2.6 | 4.9 | 5.9 |
| 95% CI | 0.9 to 1.8 | 1.8 to 2.0 | 2.2 to 3.5 | 2.0 to 3.5 | 3.0 to 10.5 | 5.9 to 6.1 |

**FIG 3.** Immunophenotype. (A) Of the 110 patients with *NRG1* fusion–positive lung cancers, PD-L1 status was known in 46 patients as shown in the pie chart on the left. Of these 46 patients, PD-L1 expression is divided into 0%, 1%-49%, and ≥ 50%, the frequencies of which are shown in the pie chart on the right. The size of the pie

**TABLE 2.** Activity of Systemic Therapy

| Response | Platinum-Doublet–Based Chemotherapy | Taxane-Based Chemotherapy | Combined Chemotherapy and Immune Therapy | Single-Agent Immunotherapy | Targeted Therapy With Afatinib |
|---|---|---|---|---|---|
| Response rate, % | 13 | 14 | 0 | 20 | 25 |
| CR, % (n/N) | 0 (0/15) | 0 (0/7) | 0 (0/9) | 0 (0/5) | 0 (0/20) |
| PR, % (n/N) | 13 (2/15) | 14 (1/7) | 0 (0/9) | 20 (1/5) | 25 (5/20) |
| SD, % (n/N) | 47 (7/15) | 14 (1/7) | 44 (4/9) | 20 (1/5) | 15 (3/20) |
| PD, % (n/N) | 40 (6/15) | 71 (5/7) | 56 (5/9) | 60 (3/5) | 60 (12/20) |
| Median PFS (95% CI), range | 5.8 months (2.2 to 9.8), 0.7-12.1 | 4.0 months (0.8 to 5.3), 0.8-5.5 | 3.3 months (1.4 to 6.3), 1.4-15.2 | 3.6 months (0.9 to undefined), 0.9-11.2 | 2.8 months (1.9 to 4.3), 0.3-25.3 |

Abbreviations: CR, complete response; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

screening for this driver should not be biased solely toward IMAs.

From a diagnostic perspective, *NRG1* fusions can be difficult to detect using DNA sequencing alone.[23,31] In our series, only 27% of patients with *NRG1* fusion–positive tumors were identified through DNA-based testing, whereas 73% of patients primarily required RNA-based testing to identify these alterations. The design of this registry did not allow a diagnostic performance evaluation of DNA-based and/or RNA-based testing for *NRG1* detection. Specifically, a denominator of prospectively sequenced samples was not available to determine the true frequency of *NRG1* fusion detection by DNA versus RNA sequencing, and a proportion of samples were sequenced after DNA-based NGS returned negative for MAPK pathway drivers. Nevertheless, RNA-based assays appear to be the best molecular testing method to identify *NRG1* fusions. *NRG1* fusion breakpoints, while highly heterogenous as demonstrated here, convergently occur in large intronic regions that are challenging to tile and capture by DNA-based assays.[23] This observation is consistent with previous reports showing that even comprehensive contemporary DNA-based hybrid capture NGS can fail to identify selected fusions.[48] In contrast, RNA-based assays overcome common difficulties associated with DNA-based assays. In particular, assays such as anchored multiplex PCR are preferred over those that assess expression imbalance as some fusions may have high expression of both 3′ and 5′ ends. Furthermore, recognizing that *NRG1* fusions were found de novo with other drivers at low frequencies,[36] screening algorithms should consider *NRG1* fusion interrogation in *KRAS*-mutant disease and in other driver-positive cancers, particularly after progression on a prior matched TKI.

In our study, all 20 unique chimeric events retained the EGF domain of NRG1, which is known to bind ERBB3 and activate oncogenesis. Notably, 18 unique upstream partners were identified. The most common fusion was *CD74-NRG1*,[23] which was identified in 41% of tumors, with *SLC3A2-NRG1* being the second most common, found in 20% of tumors. Importantly, we identified previously unreported upstream partners, including *FGFR1*, *CADM1*, *F11R*, *FLYWCH1*, *KRAS*, and *PLCG2*; this highlights the molecular diversity of *NRG1* fusions and the need to screen for these oncogenes with a comprehensive assay poised to detect all possible rearrangements. Furthermore, *NRG2α* fusions have been identified in cancers, including NSCLCs.[49,50] These clinical observations are informative for preclinical experiments that explore fusion diversity and their ability to localize subcellularly and operate differentially in tumor cells.[19,31,48,51-53]

The most striking observation in this series is the limited lack of activity of systemic therapy in advanced *NRG1* fusion–positive lung cancers, acknowledging the small number of patients treated with selected regimens. Response to platinum-based or taxane-based post–platinum-doublet chemotherapy was poor relative to the historic activity of these agents in previously published registrational data sets that treated unselected NSCLCs. It is thus unsurprising that the median OS for patients with stage IV disease was 15.5 months. The lack of response to platinum-based chemotherapy is of interest, given that other fusion-positive tumors, such as those involving *ALK*, *ROS1*, and *RET*, are known to be sensitive to first-line chemotherapy, particularly regimens that include pemetrexed.[14,54-57]

As with other fusion-positive NSCLCs, *NRG1* fusion–positive lung cancers derived limited benefit from immunotherapy.[58-62] Response was rare and only observed in one patient of those who received either single-agent immune checkpoint inhibition or immunotherapy combined with chemotherapy. This was most surprising in the

**FIG 3.** (Continued). graphs relative to each other is not scaled to the total size of the corresponding populations. (B) Violin plots of TMB in mutations per megabase are shown for patients with *NRG1* fusion–positive lung cancers compared with those that harbor *ALK*, *ROS1*, *RET*, or *NTRK1/2/3* fusions and those whose lung cancers do not harbor these alterations (gray). The circles and black bars indicate the median and 95% CIs, respectively. PD-L1, programmed death ligand-1; TMB, tumor mutational burden.

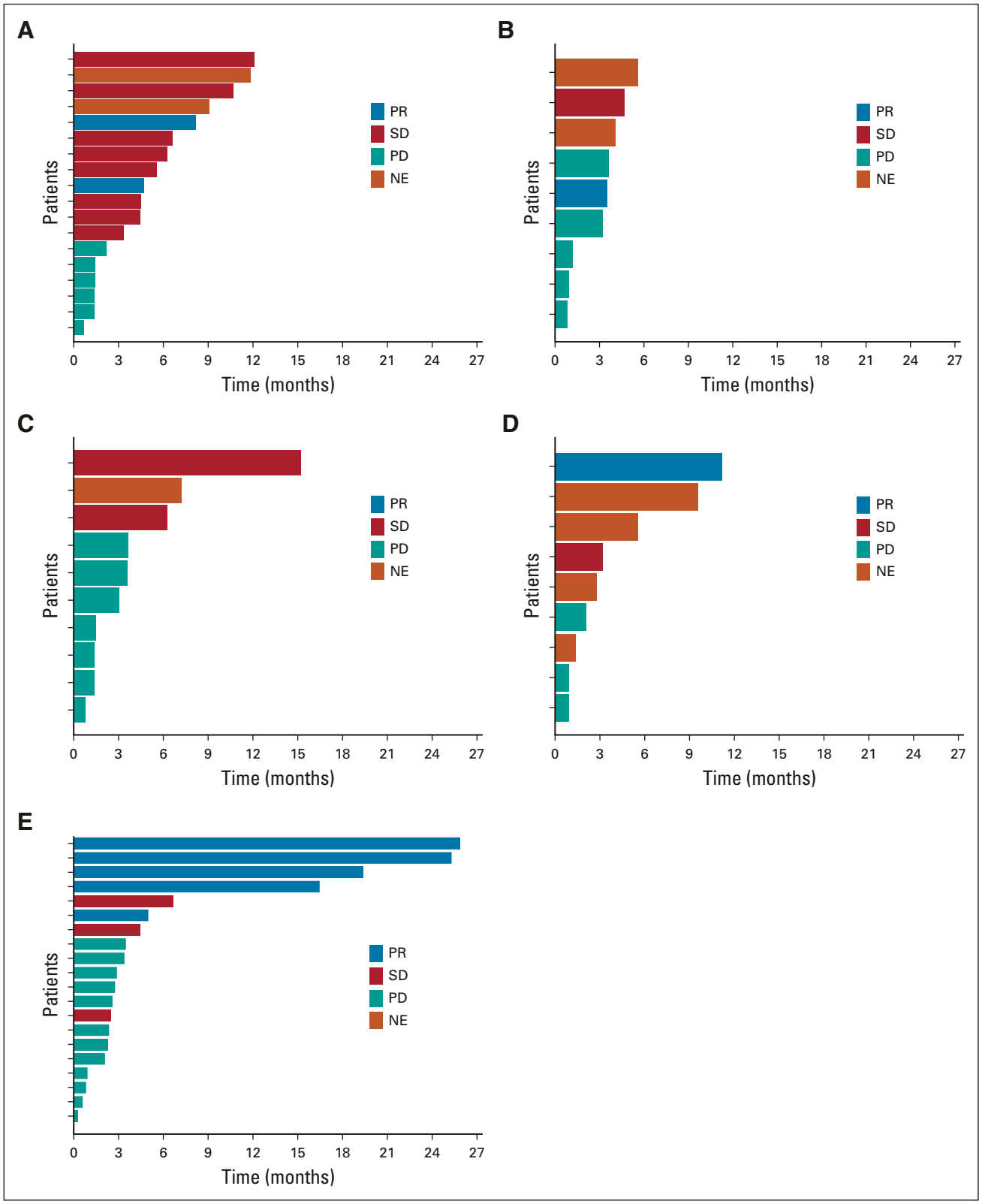



**FIG 4.** Systemic therapy activity. Swimmer plots of the duration of therapy are shown. Best response to therapy is indicated by the blue (PR), red (SD), and teal (PD) bars. Note that no patients had complete responses. The duration of treatment for patients for whom best response could not be evaluated (such as those with nonmeasurable disease) is shown in orange. Plots are separated into patients who received (A) platinum-doublet chemotherapy (n = 18), (B) taxane-based chemotherapy after prior platinum-doublet chemotherapy (n = 9), (C) combination immune checkpoint inhibition and chemotherapy (n = 10), (D) single-agent immune checkpoint inhibition (n = 9), and (E) targeted therapy with the pan-ERBB family inhibitor, afatinib (n = 20). NE, could not be evaluated; PD, progressive disease; PR, partial response; SD, stable disease.

latter group of patients for whom progressive disease was observed in more than half of patients. The lack of efficacy was consistent, however, with the immunophenotypic profile of *NRG1* fusion–positive tumors in our registry. TMB was not only lower than that in unselected NSCLCs but also interestingly lower in comparison with *ALK*, *ROS1*, *RET*, and *NTRK1/2/3* fusion–positive lung cancers. The biologic reasons that underlie such an observation remain unknown and will need to be explored. On top of this, most tumors did not express PD-L1, and only a minority (4%) of cancers had PD-L1 expression of 50% or greater, similar to *NRG2α* fusions.[50]

Disappointingly, the activity of targeted therapy with afatinib was also modest. The response rate of 25% and the median PFS of 2.8 months were substantially less than those observed with highly active contemporary targeted therapeutics for *ALK*, *ROS1*, *RET*, and *NTRK1/2/3* fusion–positive cancers.[4] Although the multicenter Targeted Agent and Profiling Utilization Registry trial (ClinicalTrials.gov identifiers: NCT02925234, NCT02693535)[63] will help confirm the prospective activity of afatinib in this setting, novel therapeutics should continue to be explored for these tumors.[22,23,25-29,64] For example, promising preclinical and/or clinical activity has been seen with ERBB3 (seribantumab, NCT04383210) or ERBB3/ERBB2 (zenocutuzumab, NCT02912949) monoclonal antibody–based therapy and pan-ERBB covalent TKI therapy (tarloxotinib, NCT03805841) in *NRG1* fusion–positive tumors.[4,22,23,25,26,44,53] Targeting *NRG2α* fusion–positive cancers may, in contrast, require strategies that take into account that these fusions may preferentially bind ERBB4.[50]

In conclusion, *NRG1* fusions have a diversity of fusion partners and an EGF binding domain that binds ERBB3. Detection should focus on the inclusion of RNA-based sequencing, which maximizes the likelihood of fusion identification. *NRG1* fusion–positive cancers typically do not express high levels of PD-L1 and have a low TMB, consistent with their poor response to immunotherapy. Furthermore, responses to chemotherapy or targeted therapy with afatinib are underwhelming. The development of novel therapeutics for these cancers is thus an unmet need.


## AFFILIATIONS

[1]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY
[2]Respiratory Department, Louis Pradel Hospital, Hospices Civils de Lyon Cancer Institute, Lyon, France
[3]Anticancer Antibodies Laboratory, Cancer Research Center of Lyon, Lyon, France
[4]Université Claude Bernard Lyon UMR INSERM 1052 CNRS 5286, Université de Lyon, Lyon, France
[5]National Cancer Center, Korea, Goyang-si, South Korea
[6]Pangaea Oncology, Quiron-Dexeus University Institute, Barcelona, Spain
[7]Institute for Health Science Research Germans Trias i Pujol (IGTP), Badalona, Spain
[8]Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan
[9]Memorial Sloan Kettering Cancer Center, New York, NY
[10]Fudan University Shanghai Cancer Center, Shanghai Medical College, Fudan University, Shanghai, China
[11]State Key Laboratory of Genetic Engineering, School of Life Sciences, Institute of Thoracic Oncology, Fudan University, Shanghai, China
[12]Pangaea Oncology, Laboratory of Molecular Biology, Quiron-Dexeus University Institute, Barcelona, Spain
[13]Université de Paris, Centre de Recherche des Cordeliers, Sorbonne Université, INSERM, Paris, France
[14]Team Inflammation, Complement, and Cancer, and Oncology Thoracic Unit Pulmonology Department, AP-HP, Hôpital Cochin, Paris, France
[15]Department of Pneumology, Lungenklinik Heckeshorn, Helios Klinikum Emil von Behring, Valence, France
[16]Karolinska Institute and Karolinska University Hospital Solna, Stockholm, Sweden
[17]Centre for Research and Development, Uppsala University/Region Gävleborg, Gävle, Sweden
[18]Local Health Authority of Romagna, Infermi Hospital, Rimini, Italy
[19]Local Health Authority of Romagna, St Maria delle Croci Hospital, Ravenna, Italy
[20]Foundation Medicine Inc, Cambridge, MA
[21]Department of Pulmonology, Hôpital Tenon, Assistance Publique Hôpitaux de Paris, Paris, France
[22]Hopital Nord Ouest Villefranche sur Saône, Gleizé, France
[23]Department of Pneumology, Klinikum Emil von Behring, Berlin, Germany
[24]Centre Hospitalier Intercommunal de Créteil, Créteil, France
[25]National Taiwan University Hospital and College of Medicine, National Taiwan University, Taipei, Taiwan
[26]New York University Langone Health Perlmutter Cancer Center, New York, NY
[27]Léon Bérard Cancer Center, Lyon, France
[28]Chao Family Comprehensive Cancer Center, Department of Medicine, Division of Hematology/Oncology, University of California, Irvine School of Medicine, Orange, CA
[29]Karmanos Cancer Institute, Wayne State University, Detroit, MI
[30]Division of Neurology, Department of Internal Medicine, St Marianna University, Kawasaki, Japan
[31]Division of Medical Oncology, University of Colorado Cancer Center, Aurora, CO
[32]Chao Family Comprehensive Cancer Center, University of California Irvine Medical Center, Orange, CA
[33]Clinique de Pneumologie, Pôle Médecine Aiguë Communautaire, Centre Hospitalier Universitaire de Grenoble, Grenoble, France
[34]Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Badalona, Spain
[35]Laboratory of Oncology, Fondazione IRCCS Casa Sollievo della Sofferenza, Foggia, Italy
[36]Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC
[37]Department of Pneumology and Thoracic Oncology, Assistance Publique-Hopitaux de Paris, Tenon Hospital and GRC Theranoscan Sorbonne Université, Paris, France

## CORRESPONDING AUTHOR

Alexander Drilon, MD, Department of Medicine, Memorial Sloan Kettering Cancer Center, 300 E 66th St, BAIC 1203, New York, NY 10065; e-mail: drilona@mskcc.org.

## EQUAL CONTRIBUTION

A.D., M.D., S.V.L., and J.C. contributed equally to this work.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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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## AUTHOR CONTRIBUTIONS

**Conception and design:** Alexander Drilon, Michael Duruisseaux, Haiquan Chen, Fanny Magne, Maria Arcila, Rafael Rosell, Stephen V. Liu, Jacques Cadranel

**Administrative support:** Christina Falcon, Rafael Rosell

**Provision of study materials or patients:** Michael Duruisseaux, Ji-Youn Han, Masaoki Ito, Miguel Angel Molina, Marie Wislez, Clarisse Dupont, Valérie Gounant, Alison M. Schram, Joshua Sabari, Robert Doebele, D. Ross Camidge, D. Ross Camidge, Sai-Hong Ignatius Ou, Denis Moro-Sibilot, Stephen V. Liu, Jacques Cadranel

**Collection and assembly of data:** Alexander Drilon, Michael Duruisseaux, Ji-Youn Han, Masaoki Ito, Christina Falcon, Morihito Okada, Miguel Angel Molina, Marie Wislez, Philippe Brun, Clarisse Dupont, Eva Branden, Giulio Rossi, Alexa Schrock, Siraj Ali, Valérie Gounant, Fanny Magne, Torsten Gerriet Blum, Alison M. Schram, Isabelle Monnet, Jin-Yuan Shih, Joshua Sabari, Maurice Pérol, Misako Nagasaka, Robert Doebele, D. Ross Camidge, Maria Arcila, Sai-Hong Ignatius Ou, Denis Moro-Sibilot, Lucia Anna Muscarella, Stephen V. Liu, Jacques Cadranel

**Data analysis and interpretation:** Alexander Drilon, Michael Duruisseaux, Ji-Youn Han, Christina Falcon, Soo-Ryum Yang, Yonina R. Murciano-Goroff, Miguel Angel Molina, Fanny Magne, Alison M. Schram, Jin-Yuan Shih, Joshua Sabari, Maurice Pérol, Viola W. Zhu, Misako Nagasaka, Robert Doebele, Maria Arcila, Sai-Hong Ignatius Ou, Stephen V. Liu, Jacques Cadranel

**Manuscript writing:** All authors

**Final approval of manuscript:** All authors

**Accountable for all aspects of the work:** All authors

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Clinicopathologic Features and Response to Therapy of *NRG1* Fusion–Driven Lung Cancers: The eNRGy1 Global Multicenter Registry**

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**Alexander Drilon**
**Honoraria:** Medscape, OncLive, PeerVoice, Physicans' Education Resource, Targeted Oncology, MORE Health, Research to Practice, Foundation Medicine, Peerview
**Consulting or Advisory Role:** Ignyta, Loxo, TP Therapeutics, AstraZeneca, Pfizer, Blueprint Medicines, Genentech/Roche, Helsinn Therapeutics, BeiGene, Hengrui Therapeutics, Exelixis, Bayer, Tyra Biosciences, Verastem, Takeda/Millennium, BerGenBio, MORE Health, Lilly, Verastem, AbbVie, 14ner Oncology/Elevation Oncology, Remedica, Archer, Monopteros Therapeutics, Novartis, EMD Serono/Merck, Melendi, Repare Therapeutics
**Research Funding:** Foundation Medicine
**Patents, Royalties, Other Intellectual Property:** Wolters Kluwer (royalties for Pocket Oncology)
**Other Relationship:** Merck, GlaxoSmithKline, Teva, Taiho Pharmaceutical, Pfizer, PharmaMar, Puma Biotechnology

**Michael Duruisseaux**
**Consulting or Advisory Role:** AstraZeneca, MSD Oncology, BMS, Pfizer, Roche, Takeda, Boehringer Ingelheim, Janssen Oncology, Amgen, AbbVie
**Travel, Accommodations, Expenses:** Boehringer Ingelheim, Merck Sharp & Dohme

**Ji-Youn Han**
**Honoraria:** Roche, AstraZeneca, Bristol Myers Squibb, Takeda
**Consulting or Advisory Role:** MSD Oncology, AstraZeneca, Bristol Myers Squibb, Lilly, Novartis, Takeda, Pfizer
**Research Funding:** Roche, Pfizer, Ono Pharmaceutical, Takeda

**Soo-Ryum Yang**
**Consulting or Advisory Role:** Invitae

**Yonina R. Murciano-Goroff**
**Travel, Accommodations, Expenses:** AstraZeneca

**Morihito Okada**
**Speakers' Bureau:** Taiho Pharmaceutical, Johnson & Johnson, Covidien, Lilly, Chugai Pharma, AstraZeneca, Ono Pharmaceutical, CSL Behring
**Research Funding:** Taiho Pharmaceutical, Nippon Kayaku, Chugai Pharma, Covidien, Johnson & Johnson, Daiichi Sankyo, Yakult Honsha, Lilly Japan, Nihon Medi-Physics, Pfizer, Mochida Pharmaceutical Co Ltd, Shionogi, Ono Pharmaceutical, Kyowa Hakko Kirin

**Miguel Angel Molina**
**Employment:** Pangaea Oncology
**Research Funding:** AstraZeneca, Merck Serono, In3Bio

**Marie Wislez**
**Consulting or Advisory Role:** Boehringer Ingelheim, Roche, MSD Oncology, Bristol Myers Squibb, AstraZeneca, Amgen
**Speakers' Bureau:** Boehringer Ingelheim, Amgen, Roche, MSD Oncology, Bristol Myers Squibb, AstraZeneca
**Travel, Accommodations, Expenses:** Roche, MSD Oncology

**Alexa Schrock**
**Employment:** Foundation Medicine
**Stock and Other Ownership Interests:** Foundation Medicine, Roche

**Siraj Ali**
**Employment:** EQRX (I), Foundation Medicine, EQRX
**Leadership:** Incysus Inc, Elevation Oncology, Pillar Biosciences
**Stock and Other Ownership Interests:** Exelixis, Merus NV, Pfizer
**Consulting or Advisory Role:** Azitra (I), Princepx Tx (I)
**Patents, Royalties, and Other Intellectual Property:**Patents via Seres Health on microbiome in non neoplastic disease (I), Foundation Medicine

**Valérie Gounant**
**Consulting or Advisory Role:** Bristol Myers Squibb, Takeda, Roche, AstraZeneca, Boehringer Ingelheim, Novartis, Chugai Pharma Europe
**Travel, Accommodations, Expenses:** Takeda, Roche, Pfizer

**Alison M. Schram**
**Research Funding:** Merus, Kura Oncology, Surface Oncology, AstraZeneca, Lilly, Northern Biologics, Pfizer, Black Diamond Therapeutics, BeiGene, Relay Therapeutics

**Isabelle Monnet**
**Travel, Accommodations, Expenses:** MSD Oncology, Roche, Takeda, Pfizer

**Jin-Yuan Shih**
**Honoraria:** AstraZeneca, Boehringer Ingelheim, Pfizer, Novartis, Merck Sharp & Dohme, Ono Pharmaceutical, Bristol Myers Squibb, Roche, Chugai Pharma, Lilly
**Consulting or Advisory Role:** Chugai Pharma, Boehringer Ingelheim, Bristol Myers Squibb, Roche, AstraZeneca, Lilly, Takeda, CStone Pharmaceuticals, Janssen Oncology, Novartis, Pfizer, Ono Pharmaceutical, Merck Sharp & Dohme
**Research Funding:** Roche
**Travel, Accommodations, Expenses:** Bristol Myers Squibb, Pfizer, Chugai Pharma, Roche

**Joshua Sabari**
**Consulting or Advisory Role:** AstraZeneca, Janssen Oncology, Navire, Pfizer, Regeneron, Medscape, Takeda

**Maurice Pérol**
**Consulting or Advisory Role:** Lilly, Roche/Genentech, Pfizer, AstraZeneca, Boehringer Ingelheim, Merck Sharp & Dohme, Bristol Myers Squibb, Novartis, Amgen, Takeda, Chugai Pharma, Gritstone Oncology
**Research Funding:** AstraZeneca, Roche, Takeda, Boehringer Ingelheim
**Travel, Accommodations, Expenses:** AstraZeneca, Roche, Bristol Myers Squibb, Merck Sharp & Dohme, Pfizer, Takeda, Chugai Pharma

**Viola W. Zhu**
**Stock and Other Ownership Interests:** TP Therapeutics
**Honoraria:** AstraZeneca, Roche/Genentech, Takeda, Blueprint Medicines, Xcovery
**Consulting or Advisory Role:** AstraZeneca, Takeda, TP Therapeutics, Roche/Genentech, Xcovery
**Speakers' Bureau:** AstraZeneca, Roche/Genentech, Takeda, Blueprint Medicines
**Travel, Accommodations, Expenses:** AstraZeneca, Roche/Genentech, Takeda, TP Therapeutics

**Misako Nagasaka**
**Consulting or Advisory Role:** AstraZeneca, Caris Life Sciences, Daiichi Sankyo, Takeda, Novartis, EMD Serono
**Speakers' Bureau:** Blueprint Medicines
**Research Funding:** Tempus
**Travel, Accommodations, Expenses:** Anheart Therapeutics

**Robert Doebele**
**Employment:** Rain Therapeutics
**Leadership:** Rain Therapeutics
**Stock and Other Ownership:** Rain Therapeutics
**Consulting or Advisory Role:** GreenPeptide, AstraZeneca, Roche/Genentech, Bayer, Takeda, Rain Therapeutics, Anchiano, Blueprint Medicines, Foundation Medicine, Guardant Health
**Patents, Royalties, and Other Intellectual Property:** Abbott Molecular for Patent PCT/US2013/057495, Rain Therapeutics, Genentech (Inst), Foundation Medicine (Inst), Black Diamond (Inst), Pearl River (Inst), Voronoi (Inst)
**Travel, Accommodations, Expenses:** Rain Therapeutics, Roche/Genentech

**D. Ross Camidge**
**Honoraria:** Roche, Takeda, AstraZeneca, Daiichi Sankyo, Bio-Thera, Ribon Therapeutics, Bristol Myers Squibb, Inivata, AbbVie, Apollomics, Elevation Oncology, EMD Serono, Helsinn Therapeutics, Lilly, Nuvalent Inc, Seattle Genetics, Turning Point Therapeutics, Kestrel Labs, Amgen Astellas BioPharma, Anchiano, Eisai, GlaxoSmithKline, Janssen, OnKure, Mersana, Pfizer, QiLu Pharmaceutical, Sanofi
**Research Funding:** Takeda

**Maria Arcila**
**Honoraria:** Invivoscribe, Biocartis
**Consulting or Advisory Role:** AstraZeneca
**Travel, Accommodations, Expenses:** AstraZeneca, Invivoscribe, Raindance Technologies

**Sai-Hong Ignatius Ou**
**Stock and Other Ownership Interests:** Turning Point Therapeutics, Elevation Oncology
**Honoraria:** Pfizer, Roche Pharma AG, Genentech/Roche, ARIAD/Takeda, AstraZeneca
**Consulting or Advisory Role:** Pfizer, Roche/Genentech, AstraZeneca, Takeda, Jassen/JNJ
**Speakers' Bureau:** AstraZeneca, Genentech/Roche
**Research Funding:** Pfizer, Roche Pharma AG, AstraZeneca/MedImmune, AstraZeneca, ARIAD, Revolution Medicines, Mirati Therapeutics, Jassen/JNJ

**Denis Moro-Sibilot**
**Consulting or Advisory Role:** Roche/Genentech, Boehringer Ingelheim, Lilly/ImClone, Sanofi, Novartis, Amgen, Pfizer, AstraZeneca, Clovis Oncology, MSD Oncology, ARIAD, Bristol-Myers Squibb, Takeda, Abbvie
**Research Funding:** Abbvie (Inst), Boehr (Inst), Roche/Genentech (Inst), Bristol-Myers Squibb (Inst)
**Expert Testimony:** MSD Oncology
**Travel, Accommodations, Expenses:** Roche/Genentech, Lilly/ImClone, Pfizer, MSD Oncology, Bristol-Myers Squibb

**Lucia Anna Muscarella**
**Travel, Accommodations, Expenses:** Boehringer Ingelheim

**Stephen V. Liu**
**Consulting or Advisory Role:** Genentech, Pfizer, Lilly, Bristol Myers Squibb, AstraZeneca, Takeda, Regeneron, G1 Therapeutics, Guardant Health, Janssen Oncology, MSD Oncology, Jazz Pharmaceuticals, Blueprint Medicines, Inivata, PharmaMar, Daiichi Sankyo/UCB Japan, BeiGene, Amgen
**Research Funding:** Genentech/Roche, Pfizer, Corvus Pharmaceuticals, Bayer, Merck, Lycera, AstraZeneca, Molecular Partners, Blueprint Medicines, Lilly, Rain Therapeutics, Alkermes, Bristol Myers Squibb, Turning Point Therapeutics, RAPT Therapeutics, Merus, Debiopharm Group, Elevation Oncology
**Travel, Accommodations, Expenses:** AstraZeneca, Roche/Genentech, MSD Oncology

**Jacques Cadranel**
**Honoraria:** AstraZeneca/MedImmune, Bristol Myers Squibb, Roche/Genentech, Merck Sharp & Dohme, Boehringer Ingelheim
**Consulting or Advisory Role:** AstraZeneca/MedImmune, Roche/Genentech, Boehringer Ingelheim, Bristol Myers Squibb, Takeda, Merck Sharp & Dohme, Pfizer, Lilly, Novartis
**Research Funding:** Pfizer, Novartis, AstraZeneca/MedImmune

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