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Relevance and Effectiveness of Molecular Tumor Board Recommendations for Patients With Non–Small-Cell Lung Cancer With Rare or Complex Mutational Profiles

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abstract

PURPOSE Molecular tumor boards (MTBs) provide physicians with a treatment recommendation for complex tumor-specific genomic alterations. National and international consensus to reach a recommendation is lacking. In this article, we analyze the effectiveness of an MTB decision-making methodology for patients with non–small-cell lung cancer (NSCLC) with rare or complex mutational profiles as implemented in the University Medical Center Groningen (UMCG).

METHODS The UMCG-MTB comprises (pulmonary) oncologists, pathologists, clinical scientists in molecular pathology, and structural biologists. Recommendations are based on reported actionability of variants and molecular interpretation of pathways affected by the variant and supported by molecular modeling. A retrospective analysis of 110 NSCLC cases (representing 106 patients) with suggested treatment of complex genomic alterations and corresponding treatment outcomes for targeted therapy was performed.

RESULTS The MTB recommended targeted therapy for 59 of 110 NSCLC cases with complex molecular profiles: 24 within a clinical trial, 15 in accordance with guidelines (on label) and 20 off label. All but 16 recommendations involved patients with an *EGFR* or *ALK* mutation. Treatment outcome was analyzed for patients with available follow-up (10 on label and 16 off label). Adherence to the MTB recommendation (21 of 26; 81%) resulted in an objective response rate of 67% (14 of 21), with a median progression-free survival of 6.3 months (interquartile range, 3.2-10.6 months) and an overall survival of 10.4 months (interquartile range, 6.3-14.6 months).

CONCLUSION Targeted therapy recommendations resulting from the UMCG-MTB workflow for complex molecular profiles were highly adhered to and resulted in a positive clinical response in the majority of patients with metastatic NSCLC.

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INTRODUCTION

The introduction of next-generation sequencing in the analysis of different tumor types has revealed a variety of genomic alterations, often with clinical significance.[1,2] Targeted therapy toward a number of targets is now standard of care in various cancer types, most notably non–small-cell lung cancer (NSCLC).[3-8] In 2018, targeted therapy was included in guidelines for patients with NSCLC harboring *EGFR* and *BRAF* p.(V600) driver mutations, *ALK* and *ROS1* rearrangements, and the *EGFR* p.(T790M) resistance mutation.[3] Extensive molecular profiling frequently reveals uncommon or unknown (combinations of) genomic alterations as well as mutations that have not been reported in NSCLC previously, but are well described in other malignancies. This creates a challenge for the interpretation of molecular profiles and subsequent clinical decision making. The rarity of these genomic alterations renders inclusion in large clinical trials unattainable and prevents subsequent inclusion in tumor-specific guidelines.[9]

To cope with this complexity in the spectrum of genomic aberrations, multidisciplinary molecular tumor boards (MTBs) have been established to provide the best possible subsequent treatment decisions in cases of rare or unknown somatic genomic alterations.[10-19] At present, opinions vary widely on how an MTB should operate,[18] and an international consensus on how a recommendation can be achieved is lacking. There is disagreement on the type of patients eligible for discussion in an MTB, the molecular tests required to reach a conclusion, tumor types that should be included in the scope of an MTB, and the health professionals who

ASSOCIATED CONTENT

Appendix

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

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CONTEXT

Key Objective

We evaluated adherence and clinical outcome of treatment recommendations provided by a molecular tumor board (MTB) for patients with non–small-cell lung cancer (NSCLC) with rare or complex mutational profiles.

Knowledge Generated

Analysis of cases for which the MTB recommended targeted therapy revealed a high rate of adherence to the recommendation and subsequent overall response and survival rates to labeled and off-label targeted therapy.

Relevance

An MTB is effective as a tool to guide patients with NSCLC to the most appropriate targeted therapy available within the context of the health care infrastructure.

should participate in an MTB. Such differences increase the heterogeneity of MTB recommendations.[20]

The MTB of the University Medical Center Groningen (UMCG) has been operational since 2014 and receives an increasing number of requests for treatment advice. As of 2017, the requests discussed in the UMCG-MTB have been limited to rare or complex (combinations of) genomic alterations in all cancer types but predominantly NSCLC. Since 2018, molecular modeling is used as a tool to estimate the binding interactions of potential drugs to the mutated protein structures.[21,22]

Here, we present a retrospective analysis of patients with NSCLC discussed in the UMCG-MTB. The effectiveness of the systematic decision-making methodology is analyzed on the basis of the adherence and treatment outcome of patients with NSCLC receiving targeted therapy on the basis of the MTB recommendation.

METHODS

Workflow of the UMCG-MTB

Pulmonary oncologists, medical oncologists, pathologists, clinical scientists in molecular pathology (molecular biologists), and structural biologists attend the weekly in-person MTB meetings. A request for an MTB review can be submitted by a treating physician, pathologist, or clinical scientist in molecular pathology responsible for creating the (molecular) pathology report. In addition, consultation requests can be made by physicians, pathologists, or clinical scientists in molecular pathology outside the hospital's regional network. These professionals may attend the meeting through live videoconferencing. Cases referred to the MTB are typically reviewed within a week of receiving a consultation request.

The molecular profile of a case submitted to the MTB is annotated by a clinical scientist in molecular pathology (Fig 1). Cases from within the hospital's regional network are typically profiled in the ISO-NEN-15189:2012–accredited UMCG molecular pathology laboratory.[23,24] Somatic variants are annotated according to the Human Genome Variant Society recommendations for the description of sequence variants.[25-27] Variants are classified as single nucleotide polymorphisms (SNPs) on the basis of the variant allele frequency in combination with a database search consulted for known SNPs (including dbSNP, ExAC, GnomAD, and the 1000 Genomes Browser).[28-31] Actionability of oncogenic variants is tiered according to the 2017 American College of Medical Genetics and Genomics (ACMG)/ASCO/College of American Pathologists (CAP) guidelines,[32] by consulting knowledge databases (cBioPortal, CIViC, ClinVar, COSMIC, JAX-CKB, and OncoKB), and by a systematic review of the literature.[33-38] Prior experience with similar cases within the MTB, including potential response to therapy, is included in this assessment. For cases bearing unknown or rare (combinations of) variants, a structural biologist performs molecular modeling, which consists of homology modeling, molecular docking, and molecular dynamics to assess the effects of the mutation(s) at the molecular level. In addition, modeling provides an estimate of efficacy (binding affinity) for available drugs that are not limited to disease indication.[21,22,39]

The MTB differentiates between samples discussed at first-line choice of therapy and samples discussed at progression. Guideline-based therapeutics are used in cases on first-line choice of therapy. When guideline-based targeted therapy is not self-evident, the MTB first considers for which nationwide available clinical trial(s) the patient may be eligible, including nontargeted therapy trials. Frequently, a drug is available within the Dutch Drug Rediscovery Protocol (DRUP).[40-42] Alternatively, available trials in the Netherlands and neighboring countries Belgium and Germany are listed in the MTB app available for Android (Google, Mountain View, CA) and iOS (Apple, Cupertino, CA). This app is linked to ClinicalTrials.gov and allows one to search for trials on the basis of tumor type and molecular alteration. When no trials are available, recommendations for off-label targeted therapy are based on the availability of evidence-based prescription of a (combination of) drug(s). Off-label targeted therapy is only considered when the evidence that supports actionability is tiered at least at level 2D (2017 ACMG/ASCO/CAP guidelines).[32] The treating

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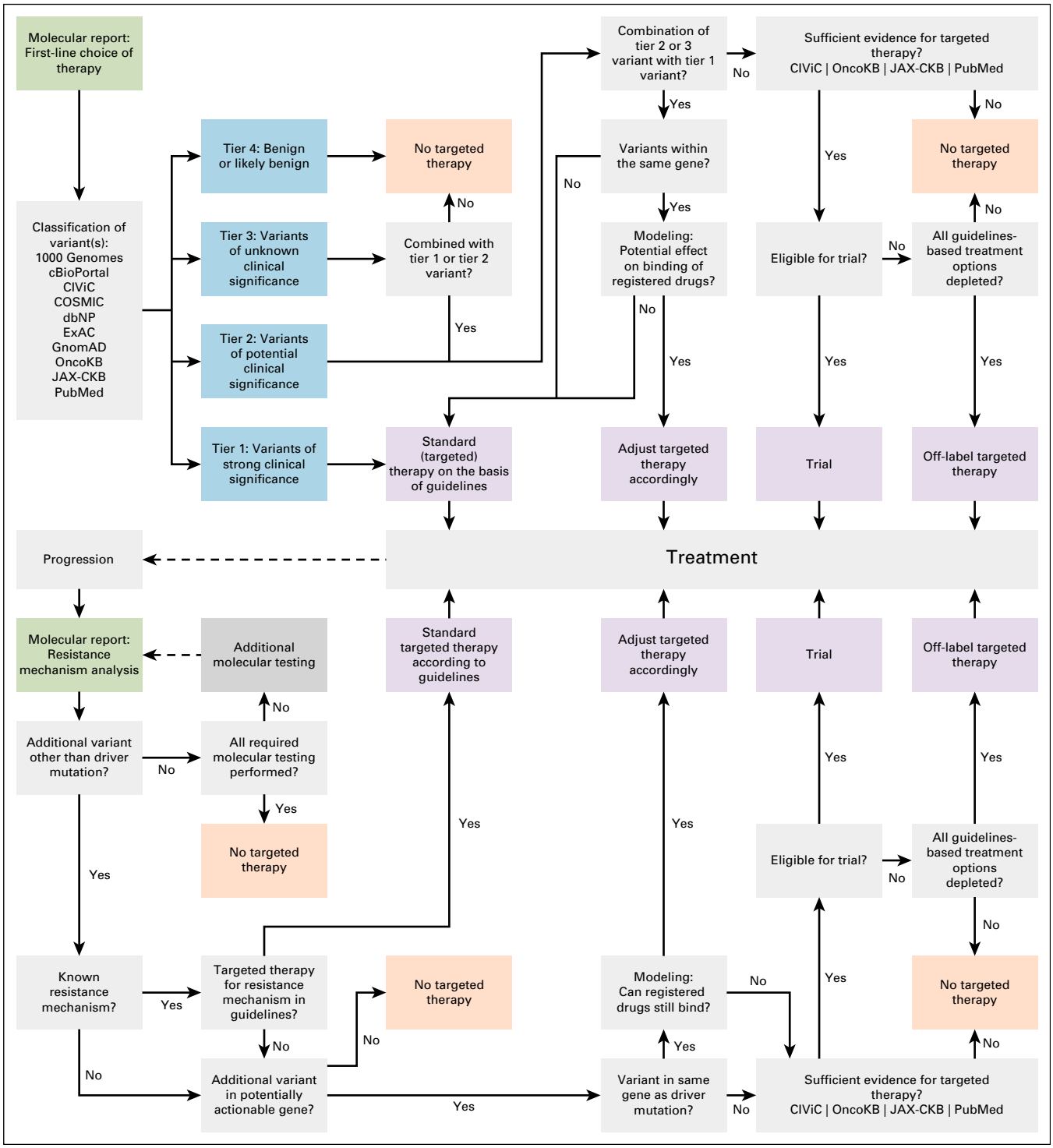

FIG 1. University Medical Center Groningen (UMCG) molecular tumor board (MTB) decision-making methodology. Flowchart illustrating the methodology of molecular-guided decision making within the UMCG-MTB. The decision-making starts with the molecular report (obtained at first-line choice of therapy or at resistance).

pulmonary oncologist will then consider this treatment, dependent on factors such as performance status and comorbidity, as well as the potential availability of the recommended drug in named patient programs.

The results of the MTB discussion and conclusions are recorded in the hospital's medical record system. For patients under treatment outside the UMCG, the information is sent to the applicant. Furthermore, all cases

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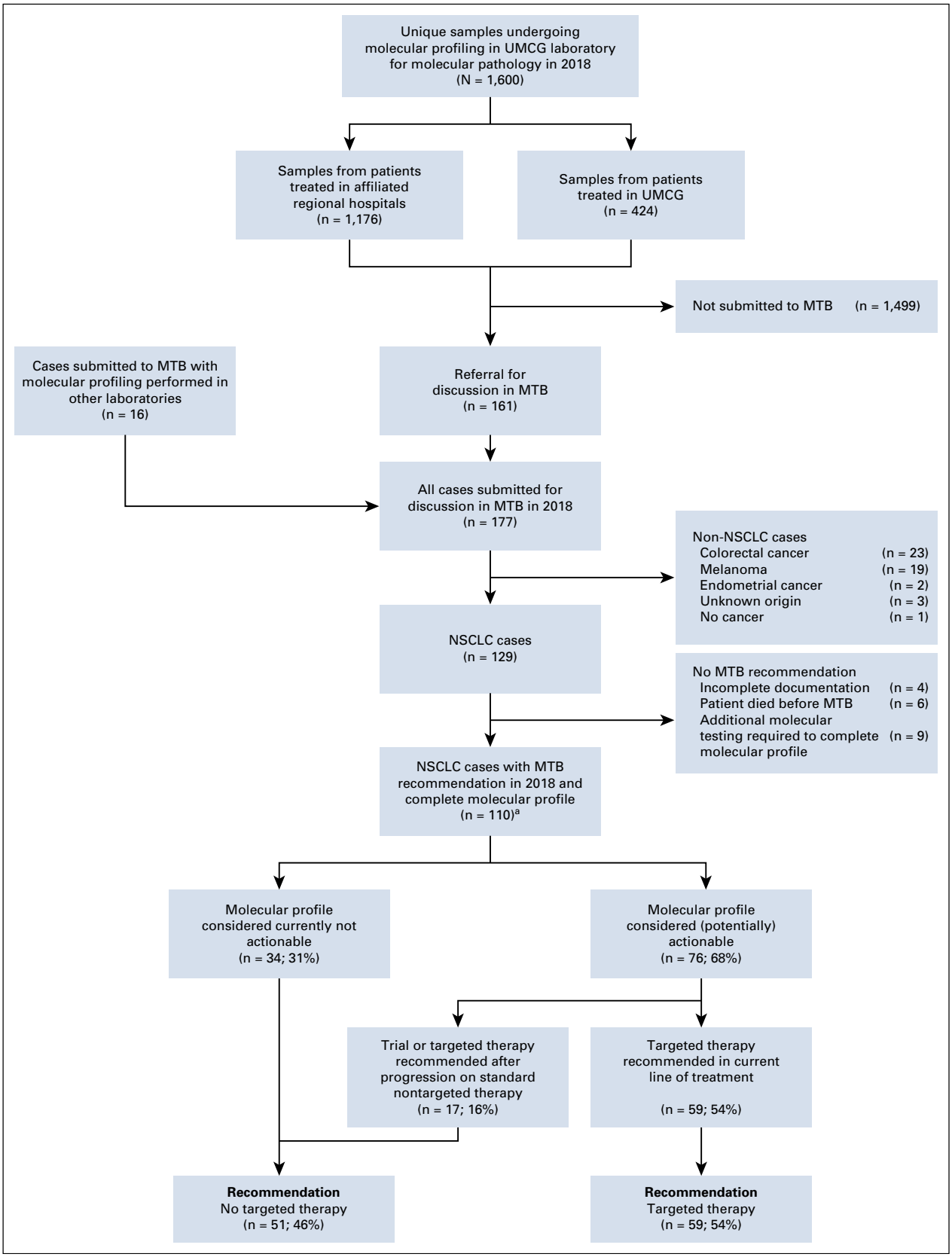

FIG 2. Case selection. Flow diagram that represents the selection of samples for analysis and subsequent molecular tumor board (MTB) recommendations. ([a]) A total of 110 samples from 106 patients; 3 patients were reviewed multiple times in 2018. In this diagram, each request for MTB review is included as a single case. NSCLC, non–small-cell lung cancer; UMCG, University Medical Center Groningen.

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reviewed by the MTB are prospectively registered in an MTB-specific database. Variables collected in this database include patient and sample identifiers, histologic classification, molecular testing results, considerations by the MTB, molecular modeling results, and the MTB recommendation.

Treatment Outcome Analysis of NSCLC Cases Reviewed by the UMCG-MTB

A treatment outcome analysis was performed for all NSCLC cases eligible for a treatment recommendation reviewed by the MTB in 2018. Follow-up data were collected retrospectively for all patients with NSCLC to analyze the effectiveness of the MTB recommendation. Informed consent was obtained from all patients. For patients recommended for inclusion in a trial, the effectiveness of an MTB recommendation was defined as adherence to this recommendation. For patients recommended for targeted therapy outside a trial, effectiveness of a recommendation was determined by adherence and corresponding treatment outcome. Targeted therapy was considered on-label therapy when a treatment was recommended that was labeled for the specific molecular indication or described in the current guidelines at the time of recommendation and off-label therapy when these criteria were not met.

Variables collected in addition to those collected in the UMCG-MTB database were the Eastern Cooperative Oncology Group performance score before the MTB discussion, the therapy regimen received after discussion, and response and survival rates since the start of treatment after MTB review. Follow-up data were retrieved from electronic health records. Clinical data processing was performed in accordance with the General Data Protection Regulation (European Union) 2016/679.

Statistics

Two primary end points were defined: adherence to the treatment recommendation and overall response rate (ORR). Secondary end points were progression-free survival (PFS) and overall survival (OS). Treatment efficacy of (targeted) therapy was determined by RECIST version 1.1.[43] The time difference between start of treatment and disease progression as determined by radiologic progression (PFS) and death (OS) was calculated for each patient using the reported dates in the electronic health records. The median PFS and OS for all patients who received targeted therapy were calculated as well as the interquartile ranges (IQRs). Best overall response is defined as best radiologically confirmed response 12 weeks after the start of treatment: progressive disease (PD), stable disease (SD), partial response (PR), or complete response (CR). Descriptive statistics were used to evaluate treatment recommendations. Calculations were performed using R version 3.6.1 software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

UMCG-MTB Recommendations for NSCLC Cases

In 2018, 177 cases with uncommon or multiple molecular alterations for which it was unclear whether the patient may benefit from targeted therapy were submitted for discussion in 47 MTB meetings (average, 3.8 cases/meeting; Fig 2). These included 111 external cases (63%) that originated from 12 affiliated regional hospitals and 2 other academic hospitals. Patients reviewed by the MTB encompassed those with NSCLC (129 of 177; 73%), colorectal cancer (23 of 177; 13%), melanoma (19 of 177; 11%), and a mix of other cancer types (6 of 177; 3%). Overall, 110 NSCLC cases (85%) that represented 106 patients with a complete molecular profile were eligible for further analysis (Table 1). Molecular modeling was performed in 22 of these cases (20%).

The MTB recommended targeted therapy in 59 cases (54%), including 35 with no prior systemic therapy and 24 with one or more prior systemic therapies (Appendix Table A1). Reasons for not recommending targeted therapy (51 of 110) were that the patient did not yet receive standard nontargeted therapy (n = 17); the reviewed variants were considered to be of unknown significance (n = 7); the evidence for actionability of the (likely) pathogenic variant

TABLE 1. Characteristics of NSCLC Cases Discussed in the UMCG-MTB in 2018

Characteristic	Cases, No. (%)
No. of cases	110
Median age, years (range)[a]	68 (36-89)
Sex	
Female	58 (52.7)
Male	38 (34.5)
Unspecified	14 (12.7)
Referring institution	
University medical center hosting the MTB	34 (30.9)
Affiliated regional hospital	72 (65.5)
Affiliated university medical centers	4 (3.6)
Prior lines of therapy	
0	75 (68.2)
≥ 1	35 (31.8)
Lung tumor histology	
Adenocarcinoma	86 (78.2)
NSCLC NOS	21 (19.1)
Squamous cell carcinoma	1 (0.9)
Adenosquamous carcinoma	1 (0.9)
Pleomorphic carcinoma	1 (0.9)

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

[a]Determined at time of MTB discussion.

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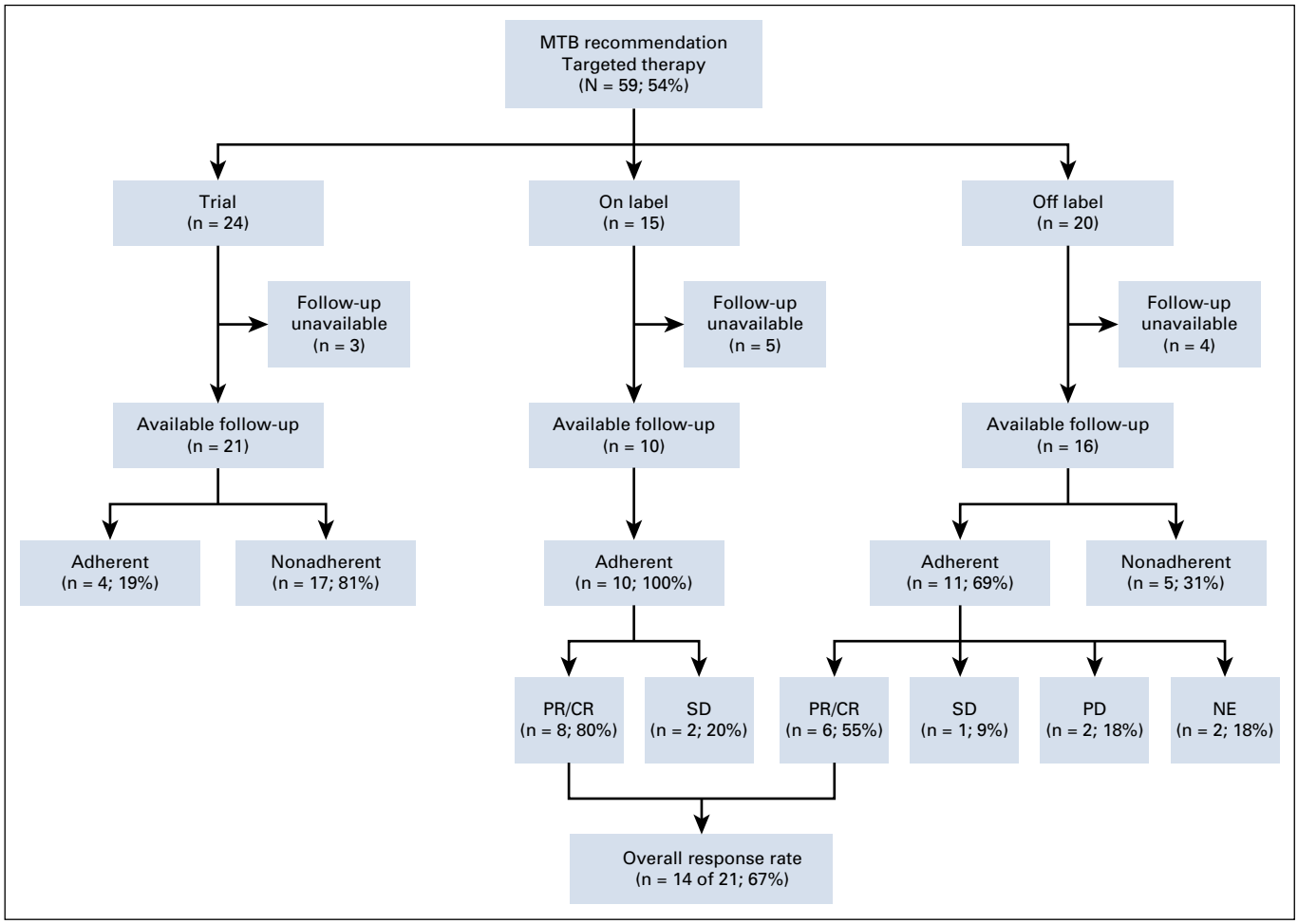

FIG 3. Adherence to molecular tumor board (MTB) recommendations and corresponding treatment outcomes. Flow diagram that represents the adherence to University Medical Center of Groningen MTB recommendations of targeted therapy and corresponding treatment outcomes for patients receiving targeted therapy outside the context of a clinical trial. CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial remission; SD, stable disease.

was tiered at level 3 or lower according to the 2017 ACGM/ASCO/CAP guidelines at the time of discussion (n = 19); or a lack of effective targeted therapy options existed for resistance-associated variants (n = 8).

Adherence to Targeted Therapy Recommendations

The 59 targeted therapy recommendations were within the context of a clinical trial (n = 24; 41%; follow-up available in 21), on-label treatment (n = 15; 25%; follow-up available in 10); or off-label treatment (n = 20; 34%; follow-up available in 16; Fig 3). Of the patients who were recommended to be included in a clinical trial, 19% (4 of 21) were enrolled in the recommended trial. Reasons for exclusion from the recommended trial included that the patient did not meet eligibility criteria or refused to participate.

Adherence to recommended targeted therapy was 100% (10 of 10) in case recommendations in accordance with current guidelines, whereas adherence to the recommended off-label targeted therapy was 69% (11 of 16). In 5 cases, the proposed treatment regimen could not be prescribed because of poor performance score, undisclosed decision by clinician and patient, or inability to obtain the drug for off-label treatment. Combined adherence to the proposed targeted therapy recommendations outside the context of a clinical trial was 81% (21 of 26).

Treatment Outcome for Patients Receiving Targeted Therapy

Cutoff for follow-up was November 14, 2019. ORR in patients receiving the recommended treatment was 67% (14 of 21; Table 2). Median PFS was 6.3 months (IQR, 3.2-10.6 months), with ongoing treatment in 4 patients (19%). Median OS was 10.4 months (IQR, 6.3-14.6 months), with 9 patients (43%) alive at last visit. Response and survival rates for patients receiving different treatment than recommended were not compared with adherent cases because of the low number of nonadherent cases and the advisory nature of the MTB, which means that final choice of therapy was at the discretion of the treating physicians and their patients.

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TABLE 2. Adherence and Treatment Outcome of 26 Patients With NSCLC With Available Follow-Up for Whom the UMCG-MTB Recommended Targeted Therapy

ID[a]	L[b]	History	Aberrations	Recommendation	Modeling	Treatment	BOR	PFS (months)	OS (months)	Status
Patients with a targeted therapy recommendation for molecular profiles not covered by current guidelines (off label; n = 16)										
5	1	*ALK* rearrangement 1L: crizotinib (CR)	*ALK* rearrangement *ALK* p.(I1171N) *ALK* p.(G1269A)	Ceritinib	Yes	Ceritinib	NE	0.72	0.72 deceased	Deceased before radiologic evaluation
12	1	*ALK* rearrangement 1L: crizotinib (PR)	*ALK* rearrangement *ALK* p.(L1196M)	Try alectinib; if progressive: brigatinib	No	Alectinib	PR	18.50	18.50 alive	Ongoing treatment with alectinib
13	2	*ALK* rearrangement 1L: crizotinib (PR) *ALK* rearrangement *ALK* p.(S1206A) 2L: brigatinib (CR)	*ALK* rearrangement *ALK* p.(S1206A) *ALK* p.(E1210K)	Alectinib or entrectinib	Yes	Alectinib	SD	2.53	4.44 deceased	After progression on alectinib, referred back to regional hospital for chemotherapy; deceased shortly thereafter
16	1	*ALK* rearrangement 1L: crizotinib (PR)	*ALK* rearrangement *ALK* p.(E1129V)	Ceritinib	Yes	Ceritinib	PR	6.34	6.34 deceased	Ongoing response at last visit; cause of death unknown
18	1	*ALK* rearrangement 1L: alectinib (PR)	*ALK* rearrangement *ALK* p.(L1196M)	Lorlatinib	Yes	Lorlatinib	PR	5.26	6.97 deceased	Deceased as a result of PD
30	2	*ALK* rearrangement 1L: crizotinib (SD) *ALK* rearrangement *ALK* p.(G1202R) (VAF 5%) 2L: MTB: alectinib (PR)	*ALK* rearrangement *ALK* p.(G1202R) (VAF 45%)	Lorlatinib	No	Lorlatinib	CR	10.58	10.58 alive	Ongoing treatment with lorlatinib
6	2	*EGFR* p.(E746_S752delinsV) 1L: gefitinib (PR) *EGFR* p.(E746_S752delinsV) *EGFR* p.(T790M) 2L: osimertinib (PR)	*EGFR* p.(G724S) *EGFR* p.(E746_S752delinsV) Loss of *EGFR* p.(T790M)	Rechallenge gefitinib	Yes	Rechallenge gefitinib	NE	0.82	0.82 deceased	Deceased before radiologic evaluation
11	2	*EGFR* p.(E746_A750del) 1L: erlotinib (PR) *EGFR* p.(E746_A750del) *EGFR* p.(T790M) 2L: osimertinib (PR)	*EGFR* p.(E746_A750del) *EGFR* p.(T790M) *EGFR* p.(C797S)	Brigatinib plus cetuximab	Yes	Local RT, continued osimertinib	SD	17.58	17.58 alive	Ongoing treatment with osimertinib
14a	1	*EGFR* p.(L8585R) 1L: erlotinib (PR)	*EGFR* p.(L858R) *ERBB2* amplification	Trastuzumab plus pertuzumab	No	Trastuzumab plus pertuzumab plus docetaxel	PR	4.83	9.66 deceased	*EGFR* p.(T790M) with loss of *ERBB2* amplification found after progression Switched to osimertinib (patient 14b)

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TABLE 2. Adherence and Treatment Outcome of 26 Patients With NSCLC With Available Follow-Up for Whom the UMCG-MTB Recommended Targeted Therapy (Continued)

ID[a]	L[b]	History	Aberrations	Recommendation	Modeling	Treatment	BOR	PFS (months)	OS (months)	Status
15a	2	*EGFR* p.(E746_A750del) 1L: gefitinib (PR) *EGFR* p.(E746_A750del) *EGFR* p.(T790M) 2L: osimertinib (PR)	*EGFR* p.(E746_A750del) *MET* amplification	Gefitinib plus crizotinib	No	Rechallenge gefitinib	PD	1.48	8.67 alive	Switched to chemotherapy after progression (patient 15b)
15b	3	As described in patient 15a	*EGFR* p.(E746_A750del) *MET* amplification	Gefitinib plus crizotinib or gefitinib plus capmatinib	No	Chemotherapy	SD	4.50	5.09 alive	Switched to palliative treatment after progression
25	3	*EGFR* p.(E746_A750del) 1L: gefitinib (PR) *EGFR* p.(E746_A750del) *EGFR* p.(T790M) 2L: osimertinib (PR) *BRAF* p.(V600E) *EGFR* p.(E746_A750del) *EGFR* p.(T790M) 3L: MTB: dabrafenib plus trametinib plus osimertinib (low dose; SD)	*EGFR* p.(E746_A750del) *EGFR* p.(C797S) Loss of *BRAF* p.(V600E) Loss of *EGFR* p.(T790M)	Rechallenge gefitinib	Yes	Rechallenge gefitinib	PD	0.95	0.95 deceased	Deceased as a result of PD within 1 month after MTB review
29	2	*EGFR* p.(E746_A750del) 1L: afatinib (PR) *EGFR* p.(E746_A750del) *EGFR* p.(T790M) 2L: osimertinib (PR)	*EGFR* p.(E746_A750del) *EGFR* p.(C797S) Loss of *EGFR* p.(T790M)	Rechallenge gefitinib	Yes	Rechallenge gefitinib	PD	1.61	11.5 alive	Switched to chemotherapy with ongoing response
31	3	1L: chemotherapy *EGFR* p.(G719A) *EGFR* p.(R776G) 2L: gefitinib (PR) *EGFR* p.(G719A) *EGFR* p.(R776G) 3L: MTB: afatinib (PR)	*EGFR* p.(G719A) *EGFR* p.(R776G) *EGFR* amplification	Afatinib plus cetuximab	No	Afatinib plus cetuximab	PR	16.1	17.02 alive	Ongoing treatment with afatinib plus cetuximab Progressed after 16 months New biopsy showed additional *EGFR* p.(T790M) Patient due to start treatment with osimertinib
19	0	—	*MET* p.(D1028N)[c]	Capmatinib	No	No therapy	—	—	0.85 alive	Patient did not desire additional therapy, no more follow-up
23	2	1L: chemotherapy 2L: pembrolizumab plus RT	*ERBB4* p.(G785V) *MET* amplification	Crizotinib	No	Afatinib	PD	0.92	1.25 deceased	Treated with afatinib instead Progression after 4 weeks Switched to crizotinib but died as a result of pneumonia after 1.5 weeks of crizotinib treatment

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TABLE 2. Adherence and Treatment Outcome of 26 Patients With NSCLC With Available Follow-Up for Whom the UMCG-MTB Recommended Targeted Therapy (Continued)

ID[a]	L[b]	History	Aberrations	Recommendation	Modeling	Treatment	BOR	PFS (months)	OS (months)	Status
Patients with a targeted therapy recommendation according to current guidelines (n = 10)										
4	0	—	*BRAF* p.(V600E)	Dabrafenib plus trametinib	No	Dabrafenib plus trametinib	SD	7.82	9.17 deceased	Switched to pembrolizumab after progression
26	2	*BRAF* p.(V600E) 1L: dabrafenib plus trametinib (PR) *BRAF* p.(V600E) 2L: atezolizumab	*BRAF* p.(V600E) *PIK3CA* p.(E542K)	Dabrafenib plus trametinib	No	Dabrafenib plus trametinib	SD	4.47	6.70 deceased	RT on new lesions after progression Deceased before restarting dabrafenib plus trametinib
2a	1	*EGFR* p.(E746_A750del) 1L: gefitinib (PR)	*EGFR* p.(E746_A750del) *EGFR* p.(T790M) *PTEN* p.(D92H)	Osimertinib	No	Osimertinib	PR	9.23	22.31 alive	Reviewed three more times in MTB (Appendix Table A1) Switched to chemotherapy after progression *PTEN* deletion found after progression Awaiting off-label treatment with everolimus plus osimertinib (MTB recommendation)
3	0	—	*EGFR* p.(E746_A750del) *MET* p.(N375S)	EGFR TKI	No	Gefitinib	PR	7.39	20.21 alive	Resistance by *EGFR* p.(T790M), treated with osimertinib, ongoing
7	0	—	*EGFR* p.(G719A) *EGFR* p.(S768I)	Afatinib	Yes	Afatinib	PR	12.65	20.01 alive	Switched to chemotherapy after progression
14b	2	As described in patient 14a	*EGFR* p.(L858R) *EGFR* p.(T790M) Loss of *ERBB2* amplification compared with preceding sample 14a	Osimertinib	No	Osimertinib	PR	3.15	3.15 deceased	Deceased as a result of pneumonia, not disease related
17	0	—	*AKT1* p.(E40K) *EGFR* p.(L858R)	EGFR TKI	No	Erlotinib	PR	10.55	12.12 alive	Progression as a result of *EGFR* p.(T790M) Treated with osimertinib, ongoing
63	0	—	*EGFR* p.(E709_T710delinsD)	EGFR TKI	Yes	Afatinib After response, switched to gefitinib because of toxicity	CR	4.83	10.38 deceased	Stopped gefitinib because of toxicity followed by progression and subsequent start of erlotinib in low dose with PR

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TABLE 2. Adherence and Treatment Outcome of 26 Patients With NSCLC With Available Follow-Up for Whom the UMCG-MTB Recommended Targeted Therapy (Continued)

ID[a]	L[b]	History	Aberrations	Recommendation	Modeling	Treatment	BOR	PFS (months)	OS (months)	Status
97	0	—	*EGFR* p.(E746_A750del) *EGFR* p.(V834L)	EGFR TKI	Yes	Gefitinib	PR	8.31	12.09 alive	Ongoing treatment Also received RT for bone metastasis
103	0	—	*EGFR* p.(D761Y) *EGFR* p.(L858R)	Afatinib, otherwise try osimertinib	Yes	Afatinib	PR	9.13	14.62 alive	Switched to chemotherapy with atezolizumab after progression

NOTE. PFS and OS are months since start of treatment or MTB review. Start of MTB review was used only in case no treatment was initiated.

Abbreviations: BOR, best overall response; CR, complete response; ID, identifier; L, line of systemic treatment; MTB, molecular tumor board; NE, not evaluable; NSCLC, non–small-cell lung cancer; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RT, radiotherapy; SD, stable disease; TKI, tyrosine kinase inhibitor; UMCG, University Medical Center Groningen; VAF, variant allele frequency.

[a]Patients discussed multiple times are indicated by a patient ID followed by a lowercase letter (a and b), with alphabetical order indicating chronology of the samples discussed.

[b]Lines of systemic therapy given before MTB review.

[c]*MET* p.(D1028N) was later confirmed to be a single nucleotide polymorphism.

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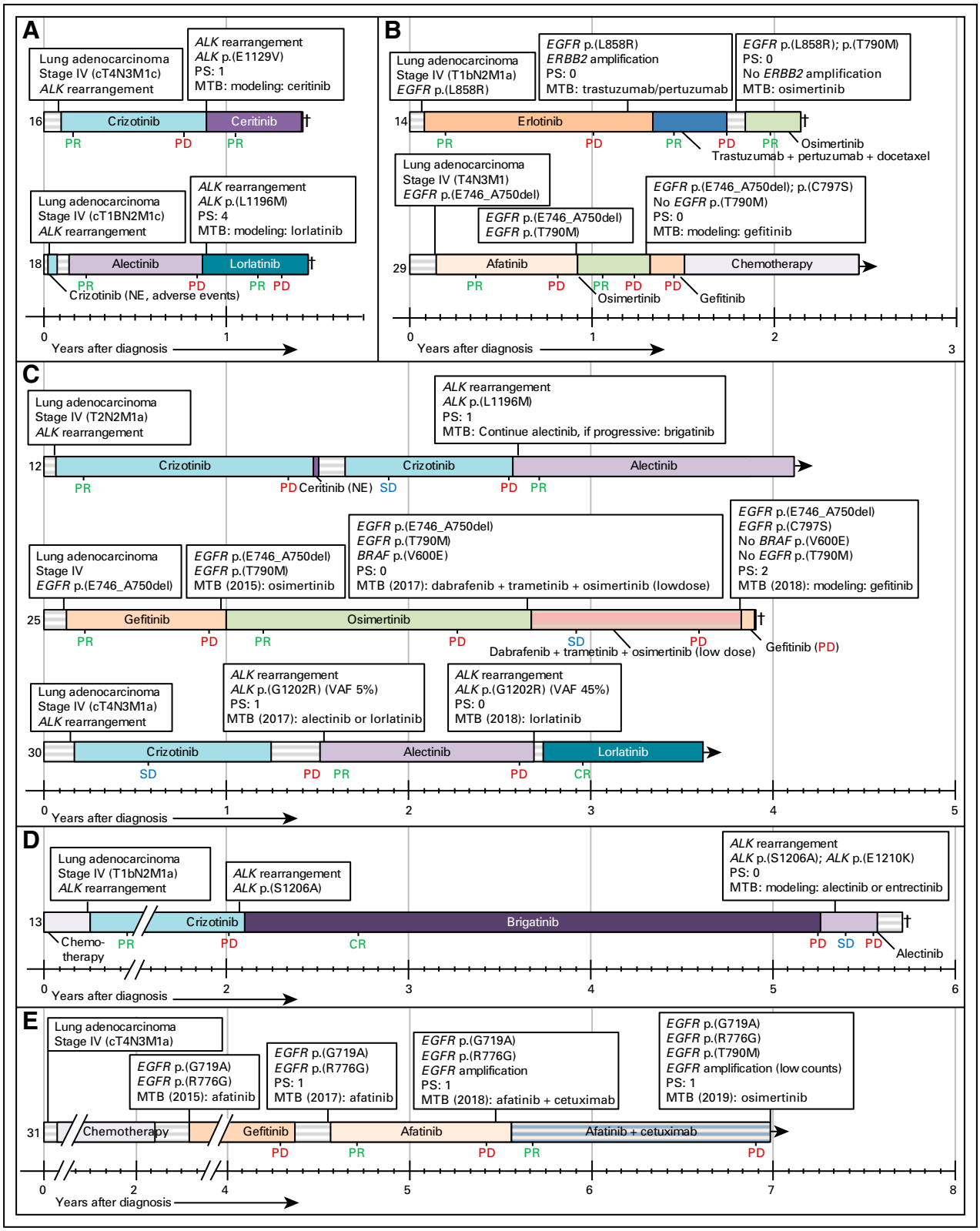

FIG 4. Off-label cases with ALK or EGFR inhibitor resistance. Swimmer plots illustrating the clinical course (in years on the *x*-axis) after diagnosis of patients with an ALK or EGFR inhibitor resistance mechanism who received off-label targeted therapy. Patients without an evaluable tumor response are not included in these plots. Patient identifiers are indicated to the left of each plot. Tumor type and stage at diagnosis are indicated. Drugs received are color coded and plotted in time; no active therapy is indicated by gray and white bars. Molecular diagnostics results are displayed at their respective points in time in a text box, including (if applicable) a molecular tumor board (MTB) (continued on following page)

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Off-label–treated patients with complete follow-up who received the recommended targeted therapy (n = 11) included those with uncommon resistance mechanisms to ALK or EGFR inhibitors (evaluable patients visualized in Fig 4). All patients had received at least 1 prior line of systemic treatment with a median of 2 prior lines (range, 1-3 lines). Treatment resulted in a PR or CR in 55% (6 of 11), SD in 9% (1 of 11), and PD in 18% (2 of 11; Table 2). In 2 patients (18%), tumor response was not evaluable. Median PFS was 4.8 months (IQR, 1.3-8.5 months), and median OS was 7 months (IQR, 3.6-12.4 months). At last visit, 3 patients had ongoing response (duration of response, 16.8, 7.92, and 14.8 months in patients 12, 30, and 31, respectively), 1 patient switched to an alternative treatment regimen because of progression, and 7 patients died.

On-label–treated patients with complete follow-up who received the recommended targeted therapy (n = 10) had typically not received prior lines of systemic treatment (true in 70%). Targeted therapy resulted in a PR or CR in 80% (8 of 10) and SD in 20% (2 of 10; Table 2). Median PFS was 8.5 months (IQR, 5.5-10.2 months), and median OS was 12.1 months (IQR, 9.5-18.7 months). At last visit, 1 on-label–treated patient had an ongoing response (duration of response, 8.3 months), 5 patients had switched to an alternative treatment regimen after progression on initial therapy, and 4 patients died (Table 2).

DISCUSSION

This study reveals the effectiveness MTB recommendations for patients with NSCLC with rare or complex mutational profiles. We have described all NSCLC cases that were submitted to the UMCG-MTB for a treatment recommendation in 2018 and present the decision-making methodology that led to the recommendation. Targeted therapy recommendations outside clinical trials resulted in a high adherence rate of the treating physician (81%), with a high ORR (67%) and long-lasting PFS and OS (6.3 and 10.4 months, respectively) in patients receiving the recommended treatment.

In contrast to clinical trials, the patient population that received targeted therapy on advice from an MTB is very heterogeneous with respect to performance status, molecular and histologic tumor characteristics, and use of one or two investigational drugs. In addition, the effectiveness of a therapy cannot be compared with an alternative therapy because patients are not randomly assigned to treatment and comparator groups. As such, it is not possible to evaluate the MTB recommendation relative to a control group. Rather, the adoption of a treatment advice by the physician and the corresponding treatment outcome was used as a surrogate to determine MTB effectiveness.

The adherence rate of 69% to the recommendations for off-label cases is high compared with other MTBs in the literature, which has ranged from 27% to 40%.[10,12,14,15] In adherent off-label cases, a PR or CR was achieved in 55%. This is high considering that the majority of these cases were reviewed at progression on multiple prior lines of systemic therapy (median, 2 prior lines; range 1-3 prior lines). In contrast, the response rate of off-label targeted therapy described by other MTBs has ranged from 13% to 30%.[10,12,14,15] The higher response rate reported here could be due to the strict on-target-only criterion for off-label targeted therapy recommendations. For example, in contrast to others,[12,15] pathways downstream of *KRAS* were not considered actionable in cases of a *KRAS* mutation. In this example, the recommendation would then be standard nontargeted therapy. The subsequent low number of eligible patients may affect the observed high response rate to off-label therapy. Furthermore, successful off-label therapy is not only determined by matching a drug to a genomic alteration but also by the health care infrastructure to support the treatment. The payment system for health care costs beyond those for drug acquisition is different around the world. In addition, the success rate of off-label therapy is largely driven by increasing insight into the molecular biology of cancer and the increasing number of available drugs over time. One can predict that MTB recommendations in years to come will prove more successful than those made in the preceding years.

Usage of molecular modeling to achieve a treatment recommendation in cases of a previously uncharacterized mutation in a potentially actionable protein is unprecedented and unique to the UMCG-MTB methodology. In most cases, the mutations analyzed with modeling were observed in those that have become resistant toward first- or second-line tyrosine kinase inhibitor therapy. Alterations in *EGFR*,[22] *ALK*,[38] and *BRAF* are currently the main genes for which molecular modeling can be performed in a clinical setting. In 2018, modeling was performed for 22 NSCLC cases (20%) in the UMCG-MTB, which led to a targeted therapy recommendation in 18 (including 11 off-label recommendations) and resulted in 11 treated patients with an ORR of 50% (Table 2). Although further validation is necessary to demonstrate the effectiveness of molecular modeling as an additional supporting tool, these patients

FIG 4. (Continued). recommendation with the most recent Eastern Cooperative Oncology Group performance score (PS). Best overall radiologic response to a drug (complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD]) are displayed beneath each plot at their respective points in time. Vital status is displayed at the end of each plot: An arrow indicates alive with disease; a dagger indicates death. (A) Patients 16 and 18 survived up to 2 years after diagnosis. (B) Patients 14 and 29 survived between 2 and 3 years after diagnosis. (C) Patients 12, 25, and 30 survived between 3 and 5 years after diagnosis. (D) Patient 13 survived between 5 and 6 years after diagnosis. (E) Patient 31 survived 7 years after diagnosis. VAF, variant allele frequency.

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illustrate the potential value of integrating modeling into the therapy decision-making process.

Before considering off-label targeted therapy for NSCLC, an MTB should first consider whether all treatment options as indicated by local treatment guidelines have been exhausted. Inclusion in a clinical trial has to be considered at all times.[12,13,16,17] As such, a clinical trial was recommended in 24 of the 59 cases. Efforts to offer overarching trials for small cohorts of patients with rare or complex molecular profiles have become available, including the US-based Targeted Agent and Profiling Utilization Registry and the Dutch DRUP.[39,40] However, the proportion of cases discussed by the UMCG-MTB that were finally enrolled in a trial was low (19%), similar to previously published MTBs (range, 7%-34%).[12,16,17] This could be due to limited availability of slots; strict inclusion criteria for these trials, such as a good performance score; and additional sample requirements (eg, the DRUP trial requires a fresh frozen tumor biopsy sample, which is not always available[42]).

The complexity of interpreting rare or complex mutations in NSCLC requires an in-depth discussion that involves at least clinical scientists in molecular pathology, pathologists, and pulmonary oncologists. These experts reach a recommendation for (targeted) treatment on the basis of current literature, knowledge databases, and modeling. The actual treatment (inclusion in a trial, on/off-label targeted therapy, chemotherapy/immunotherapy, nonsystemic therapy, or no therapy) is at the discretion of treating physicians and their patients weighed against other clinical information and patient preferences unknown to the MTB. If the patient opts for off-label therapy, it is imperative to structurally register treatment outcome to monitor that these recommendations benefit and, critically, do not harm the patient. Therefore, in addition to recommending the most appropriate therapy available, registration of clinical follow-up and making this information available to other hospitals and MTBs should be an important task for an MTB. In the Netherlands, this is conceptualized in the Predictive Analysis for Therapy (PATH) project,[44] in which all institutions that harbor an MTB collaborate.[45] Among the goals of the PATH project, a cBioPortal-based secure database is established for sharing rare molecular profiles and follow-up of patients prescribed off-label targeted therapy as well as a quality directive to which a Dutch MTB should adhere to harmonize treatment recommendations. Such efforts accelerate the development and optimization of targeted therapeutic options for patients with cancer.

In conclusion, a retrospective analysis of all patients with NSCLC reviewed with the UMCG-MTB methodology for complex or rare mutational cancer profiles revealed a high adherence to targeted therapy recommendations, with a high ORR and long-lasting PFS and OS in patients who follow the MTB recommendation. These findings demonstrate the potential clinical benefit of MTB recommendations for patients with NSCLC with tumors bearing unknown, rare, or complex (combinations of) genomic aberrations.

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APPENDIX

TABLE A1. Molecular Profiles of NSCLC Samples Discussed at the UMCG-MTB in 2018

ID	Sample Time	Variant Discussed	MTB Recommendation	Reason for Not Recommending Targeted Therapy
1	First line	*NRAS* p.(V112A)	Trial	Not applicable
2a[a]	Progression	*EGFR* p.(E746_A750del); p.(T790M); *PTEN* p.(D92H)	Targeted therapy	Not applicable
2b[a]	Progression	*EGFR* p.(E746_A750del); *PIK3CA* p.(E542K)	Standard nontargeted therapy	Resistance to targeted therapy
2c[a]	Progression	*EGFR* p.(E746_A750del); p.(T790M)	Standard nontargeted therapy	Resistance to targeted therapy
3	First line	*EGFR* p.(E746_A750del); *MET* p.(N375S)	Targeted therapy	Not applicable
4	First line	*BRAF* p.(V600E)	Targeted therapy	Not applicable
5	Progression	*ALK* rearrangement; *ALK* p.(I1171N); p.(G1269A)[b]	Targeted therapy	Not applicable
6	Progression	*EGFR* p.(G724S); p.(E746_S752delinsV); loss of p.(T790M)[b]	Targeted therapy	Not applicable
7	First line	*EGFR* p.(G719A); p.(S768I)[b]	Targeted therapy	Not applicable
9	First line	*RET* rearrangement	Trial	Not applicable
10	First line	*ERBB2* p.(V659E)	Trial	Not applicable
11	Progression	*EGFR* p.(E746_A750del); p.(T790M); p.(C797S)[b]	Targeted therapy	Not applicable
12	Progression	*ALK* rearrangement; *ALK* p.(L1196M)	Targeted therapy	Not applicable
13	Progression	*ALK* rearrangement; *ALK* p.(E1210K); p.(S1206A)[b]	Targeted therapy	Not applicable
14a[a]	Progression	*EGFR* p.(L858R); *ERBB2* amplification	Targeted therapy	Not applicable
14b[a]	Progression	*EGFR* p.(L858R); p.(T790M); loss of *ERBB2* amplification	Targeted therapy	Not applicable
15a[a]	Progression	*EGFR* p.(E746_A750del); *MET* amplification	Targeted therapy	Not applicable
15b[a]	Progression	*EGFR* p.(E746_A750del); *MET* amplification	Targeted therapy	Not applicable
16	Progression	*ALK* rearrangement; *ALK* p.(E1129V)[b]	Targeted therapy	Not applicable
17	First line	*AKT1* p.(E40K); *EGFR* p.(L858R)	Targeted therapy	Not applicable
18	Progression	*ALK* rearrangement; *ALK* p.(L1196M)[b]	Targeted therapy	Not applicable
19	First line	*MET* p.(D1028N)[c]	Targeted therapy	Not applicable
20	Progression	*MET* p.(Y1230H)	Trial	Not applicable
21	Progression	*KRAS* p.(G12D)	Trial	Not applicable
22	First line	*NRAS* p.(Q61L)	Trial	Not applicable
23	First line	*ERBB4* p.(G785V); *MET* amplification	Targeted therapy	Not applicable
24	First line	*ERBB2* p.(G776delinsVV)	Trial	Not applicable
25	Progression	*EGFR* p.(E746_A750del); p.(C797S); loss of p.(T790M) and loss of *BRAF* p.(V600E)[b]	Targeted therapy	Not applicable
26	Progression	*BRAF* p.(V600E); *PIK3CA* p.(E542K)	Targeted therapy	Not applicable
27	First line	*KRAS* p.(Q61K); *PIK3CA* p.(H1047R)	Trial	Not applicable
28	First line	*MET* amplification	Trial	Not applicable
29	Progression	*EGFR* p.(E746_A750del); p.(C797S); loss of p.(T790M)[b]	Targeted therapy	Not applicable
30	Progression	*ALK* rearrangement; *ALK* p.(G1202R)	Targeted therapy	Not applicable
31	Progression	*EGFR* p.(G719A); p.(R776G); *EGFR* amplification	Targeted therapy	Not applicable

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TABLE A1. Molecular Profiles of NSCLC Samples Discussed at the UMCG-MTB in 2018 (Continued)

ID	Sample Time	Variant Discussed	MTB Recommendation	Reason for Not Recommending Targeted Therapy
32	First line	*KRAS* p.(G12A); *PIK3CA* p.(H1047L)	Standard nontargeted therapy	Insufficient evidence of actionability
33	First line	*BRAF* p.(G466V); *POLE* p.(D287E)	Standard nontargeted therapy	Insufficient evidence of actionability
34	First line	*BRAF* p.(V600E); *PIK3CA* p.(E542K)	Targeted therapy at progression	Not applicable
35	Progression	Loss of previous *ROS1* rearrangement	Standard nontargeted therapy	Resistance to targeted therapy
36	Progression	*BRAF* p.(V600E); *KRAS* p.(G12V)	Standard nontargeted therapy	Resistance to targeted therapy
37	Progression	*AKT1* p.(E17K); *BRAF* p.(V600E)	Standard nontargeted therapy	Resistance to targeted therapy
38	First line	*ROS1* p.(G2177*)	Standard nontargeted therapy	Variant of unknown significance
39	First line	*ROS1* p.(R2126Q)	Standard nontargeted therapy	Variant of unknown significance
40	First line	*PTEN* p.(R130P)	Standard nontargeted therapy	Insufficient evidence of actionability
41	Progression	*EGFR* p.(E746_A750del); loss of p.(T790M)[b]	Standard nontargeted therapy	Resistance to targeted therapy
42	Progression	*BRAF* p.(V600E)	Standard nontargeted therapy	Resistance to targeted therapy
43	First line	*EGFR* p.(S752T)	Standard nontargeted therapy	Variant of unknown significance
44	Progression	*EGFR* p.(E746_A750del); loss of p.(T790M); possible *MDM2* amplification	Targeted therapy at progression	Nontargeted therapy preferred first
46	First line	*PIK3CA* p.(M1043I)	Targeted therapy at progression	Nontargeted therapy preferred first
47	First line	*MAP2K1* p.(K57N)	Targeted therapy at progression	Nontargeted therapy preferred first
48	First line	*KRAS* p.(G12C); *IDH1* p.(R132G)	Standard nontargeted therapy	Insufficient evidence of actionability
49	First line	*MET* c.3082+1G>A (exon 14 skipping); PDL1 100%	Trial after progression	Nontargeted therapy preferred first
50	First line	*MAP2K1* p.(L180P); *KRAS* p.(G12C)	Standard nontargeted therapy	Variant of unknown significance
51	First line	*IDH2* p.(R172M)	Standard nontargeted therapy	Insufficient evidence of actionability
52	First line	*NRAS* p.(G13R)	Trial after progression	Nontargeted therapy preferred first
53	First line	*NRAS* p.(Q61R)	Trial after progression	Nontargeted therapy preferred first
54	First line	*MET* p.(D1246H)[b]	Targeted therapy	Not applicable
55	First line	*BRAF* p.(V600E)	Targeted therapy	Not applicable
56	First line	*KIT* p.(F681I); *KRAS* p.(G12C)	Standard nontargeted therapy	Variant of unknown significance
57	First line	*MET* p.(N375S)	Targeted therapy at progression	Nontargeted therapy preferred first
58	First line	*BRAF* p.(G469V)[b]	Standard nontargeted therapy	Insufficient evidence of actionability
59	First line	*MET* p.(R970C); *RAF1* p.(L251V)	Standard nontargeted therapy	Variant of unknown significance
60	First line	*EGFR* p.(A767_V769dup)[b]	Trial	Not applicable
61	Progression	*EGFR* p.(E746_A750del); *ERBB2* amplification	Trial	Not applicable
62	First line	*EGFR* p.(G719S); p.(S768I)[b]	Targeted therapy	Not applicable
63	First line	*EGFR* p.(E709_T710delinsD)	Targeted therapy	Not applicable
64	First line	*BRAF* p.(G469S)	Standard nontargeted therapy	Insufficient evidence of actionability
65	First line	*GNAS* p.(R201S)	Trial	Not applicable
66	First line	*IDH1* p.(R132H)	Standard nontargeted therapy	Insufficient evidence of actionability
67	First line	*MET* c.3028+3A>G (exon 14 skipping fusion transcript)	Trial	Not applicable
68	First line	*MAP2K1* p.(Q56P)	Targeted therapy at progression	Nontargeted therapy preferred first
69	Progression	*EGFR* p.(L718Q); p.(L858R)[b]	Targeted therapy	Not applicable
70	First line	*MET* c.2942-1G>C (exon 14 skipping fusion transcript)	Trial	Not applicable
71	First line	*KRAS* p.(G12A); possible *ERBB2* amplification	Standard nontargeted therapy	Insufficient evidence of actionability
72	First line	*EGFR* p.(S768I)	Targeted therapy	Not applicable

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TABLE A1. Molecular Profiles of NSCLC Samples Discussed at the UMCG-MTB in 2018 (Continued)

ID	Sample Time	Variant Discussed	MTB Recommendation	Reason for Not Recommending Targeted Therapy
73	First line	*MET* c.3080+2T>A	Trial	Not applicable
74	First line	*BRAF* p.(G469A)	Standard nontargeted therapy	Insufficient evidence of actionability
75	First line	*RET* rearrangement	Trial after progression	Nontargeted therapy preferred first
76	First line	*EGFR* p.(Y772_A775dup); *KRAS* p.(A59T)	Trial	Not applicable
77	First line	*ALK* p.(R1231W); *PTEN* p.(R130*)	Standard nontargeted therapy	Insufficient evidence of actionability (*ALK* variant was considered a variant of unknown significance)
78	Progression	*BRAF* p.(V600E); PDL1 > 50%	Targeted therapy at progression	Nontargeted therapy preferred first
79	First line	*BRAF* p.(G469V)	Trial	Not applicable
80	First line	*NRAS* p.(G12C); PDL1 100%	Trial after progression	Nontargeted therapy preferred first
81	First line	*IDH1* p.(R132C); *KRAS* p.(G13C)	Standard nontargeted therapy	Insufficient evidence of actionability
82	First line	*KRAS* p.(G12_G13delinsCC)	Standard nontargeted therapy	Insufficient evidence of actionability
83	First line	*RAF1* p.(S257L)	Trial	Not applicable
84	First line	*PIK3CA* p.(E545K)	Standard nontargeted therapy	Insufficient evidence of actionability
85	Progression	*EGFR* p.(T790M); p.(C797S); p.(L858R)	Targeted therapy	Not applicable
86	First line	*KRAS* p.(G12C); p.(G13V)	Standard nontargeted therapy	Insufficient evidence of actionability
87	First line	*EGFR* p.(L747_P753delinsS); p.(A864P)[b]	Targeted therapy	Not applicable
89	First line	*PIK3CA* p.(E545K)	Targeted therapy at progression	Nontargeted therapy preferred first
90	First line	*MAP2K1* p.(K57N)	Targeted therapy at progression	Nontargeted therapy preferred first
91	First line	*MET* c.2942-19_2942-13delinsAAA	Trial after progression	Nontargeted therapy preferred first
92	First line	*PIK3CA* p.(E542Q)	Standard nontargeted therapy	Insufficient evidence of actionability
93	Progression	*EGFR* p.(L858R); *ERBB2* amplification	Trial	Not applicable
94	First line	*KRAS* p.(G12C); p.(G12V)	Standard nontargeted therapy	Insufficient evidence of actionability
95	Progression	*ALK* rearrangement; *ALK* p.(T1151M)[b]	Targeted therapy	Not applicable
96	First line	*MET* c.2888-36_2888-18del	Trial	Not applicable
97	First line	*EGFR* p.(E746_A750del); p.(V834L)[b]	Targeted therapy	Not applicable
98	First line	*MET* c.2942-35_2942-11del	Trial	Not applicable
99	First line	*MET* c.3082G>T	Trial	Not applicable
100	First line	*PIK3CA* p.(E542K)	Targeted therapy at progression	Nontargeted therapy preferred first
101	First line	*KRAS* p.(G12D); *PIK3CA* p.(E545A)	Standard nontargeted therapy	Insufficient evidence of actionability
102	First line	*KIT* p.(R420T)	Standard nontargeted therapy	Variant of unknown significance
103	First line	*EGFR* p.(D761Y); *EGFR* p.(L858R)	Targeted therapy	Not applicable
104	First line	*EGFR* p.(N771_H773dup)	Trial	Not applicable
105	First line	*BRAF* p.(G464V); *KRAS* p.(G12C)	Standard nontargeted therapy	Insufficient evidence of actionability
106	First line	*EGFR* p.(D770_P772dup)	Trial	Not applicable
107	First line	*MAP2K1* p.(K57N)	Standard nontargeted therapy	Insufficient evidence of actionability
111	Progression	*EGFR* p.(E746_A750del); p.(T790M); p.(L792H)	Targeted therapy	Not applicable
112	Progression	*ALK* rearrangement	Standard nontargeted therapy	Resistance to targeted therapy

NOTE. Sample time indicates the time point in treatment at which the MTB discussion was performed: at first-line choice of therapy or at progression after targeted therapy.

Abbreviations: ID, patient identifier; MTB, molecular tumor board; NSCLC, non–small-cell lung cancer; UMCG, University Medical Center Groningen.

[a]Patients discussed multiple times are indicated by a patient ID followed by a lowercase letter (a or b), with alphabetical order indicating chronology of the samples discussed.

[b]Alterations that were analyzed with molecular modeling.

[c]*MET* p.(D1028N) was later identified as a single nucleotide polymorphism and not a somatic mutation.

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