Characterization of Non–Small-Cell Lung Cancers With MET Exon 14 Skipping Alterations Detected in Tissue or Liquid: Clinicogenomics and Real-World Treatment Patterns

Jessica K. Lee, MS1; Russell Madison, MS1; Anthony Classon, MSc1; Ole Gjoerup, PhD1; Mark Rosenzweig, PhD1; Garrett M. Frampton, PhD1; Brian M. Alexander, MD, MPH1; Geoffrey R. Oxnard, MD1; Jeffrey M. Venstrom, MD1; Mark M. Awad, MD, PhD2; and Alexa B. Schrock, PhD1

PURPOSE MET exon 14 (METex14) skipping alterations are oncogenic drivers in non–small-cell lung cancer (NSCLC). We present a comprehensive overview of METex14 samples from 1,592 patients with NSCLC, associated clinicogenomic characteristics, potential mechanisms of acquired resistance, treatment patterns, and outcomes to MET inhibitors.

METHODS Hybrid capture–based comprehensive genomic profiling (CGP) was performed on samples from 69,219 patients with NSCLC. For treatment patterns and outcomes analysis, patients with advanced METex14-altered NSCLC were selected from the Flatiron Health-Foundation Medicine clinicogenomic database, a nationwide deidentified electronic health record–derived database linked to Foundation Medicine CGP for patients treated between January 2011 and March 2020.

RESULTS A total of 1,592 patients with NSCLC (2.3%) were identified with 1,599 METex14 alterations spanning multiple functional sites (1,458 of 60,244 tissue samples and 134 of 8,975 liquid samples). Low tumor mutational burden and high programmed death ligand 1 expression were enriched in METex14-altered samples. MDM2, CDK4, and MET coamplifications and TP53 mutations were present in 34%, 19%, 11%, and 42% of tissue samples, respectively. Comparing tissue and liquid cohorts, coalteration frequency and acquired resistance mechanisms, including multiple MET mutations, EGFR, ERBB2, KRAS, and PI3K pathway alterations, were generally similar. Positive percent agreement with the tissue was 100% for METex14 pairs collected within 1 year (n = 7). Treatment patterns showed increasing adoption of MET inhibitors in METex14-altered NSCLC after receipt of CGP results; the real-world response rate to MET inhibitors was 45%, and time to treatment discontinuation was 4.4 months.

CONCLUSION Diverse METex14 alterations were present in 2%-3% of NSCLC cases. Tissue and liquid comparisons showed high concordance and similar coalteration profiles. Characterizing common co-occurring alterations and immunotherapy biomarkers, including those present before or acquired after treatment, may be critical for predicting responses to MET inhibitors and informing rational combination strategies.

INTRODUCTION MET exon 14 skipping alterations are established drivers of oncogenesis and occur in approximately 3% of patients with non–small-cell lung cancer (NSCLC).1-3 Exon 14 encodes the juxtamembrane domain of the MET receptor tyrosine kinase, including the Y1003 residue required for efficient recruitment of the CBL E3 ubiquitin ligase, which targets MET for ubiquitin-mediated degradation.4 Heterogenous alterations in exon 14 and its adjacent introns can interfere with splicing, resulting in exon 14 skipping, or directly alter or delete the CBL binding site, leading to increased MET stability and oncogenic potential.2,4-8 MET exon 14 skipping alterations confer sensitivity to the multityrosine kinase inhibitor (TKI) crizotinib, and initial data suggest that response rates are similar across METex14 skipping alteration subtypes.9 Multiple other TKIs, including capmatinib and tepotinib, have received US Food and Drug Administration (FDA) approval for NSCLC with MET exon 14 skipping...
This study examined more than 1,500 individual patients with METex14-altered non–small-cell lung cancer allowing granular description of diverse alterations activating MET, as well as exploring coalterations and signatures, which may predict resistance and sensitivity to combination therapies.

Knowledge Generated
METex14 skipping alterations were identified via tissue and liquid biopsy, as well as a smaller subset of alterations predicted to disrupt the exon 14 CBL binding site or activate MET via other mechanisms. Coalteration observations from previous reports were confirmed in this larger data set, and targetable mechanisms of resistance to MET inhibitors were identified. Treatment patterns and outcomes using a real-world data set were also described.

Relevance
METex14 skipping alterations are targetable drivers in non–small-cell lung cancer. This study confirms the diversity of these alterations and highlights the need for rigorous methods of detection and standardization of biomarker definitions. Genomic profiling to identify coalterations and mechanisms of acquired resistance is warranted to further tailor personalized treatments.

METHODS
Foundation Medicine CGP
Hybrid capture–based CGP was performed on formalin-fixed paraffin-embedded tumor tissue or circulating tumor DNA (ctDNA) samples collected from 69,219 patients with primarily advanced NSCLC during routine clinical care. Testing was performed in a Clinical Laboratory Improvement Amendments-certified, College of American Pathologists-accredited, and New York State-regulated reference laboratory (Foundation Medicine Inc, Cambridge, MA). Approval for this study, including a waiver of informed consent and a Health Insurance Portability and Accountability Act waiver of authorization, was obtained from the Western Institutional Review Board (Protocol No. 20152817). For additional details, see Appendix 1.

Flatiron Health-Foundation Medicine Clinicogenic Database
This study used the nationwide deidentified advanced NSCLC Flatiron Health-Foundation Medicine CGDB (FH-FMI CGDB). Retrospective longitudinal clinical data were derived from electronic health records (EHR), comprising patient-level structured and unstructured data, curated via technology-enabled abstraction, and were linked to genomic data derived from FMI CGP tests by deidentified, deterministic matching. During the study period, the deidentified data originated from approximately 280 cancer clinics (approximately 800 sites of care). This study included 8,614 patients who had a diagnosis of advanced NSCLC, received care within the FH network between January 2011 and March 2020, and underwent tissue CGP (FoundationOne or FoundationOne CDx) between August 2012 and March 2020. Institutional Review Board approval with waiver of informed consent was obtained before conducting the study. For additional details, see Appendix 1.
patients (2.3%). MEx14 alterations were identified in 2.4% (1,458 of 60,244) of tissue specimens and 1.8% (134 of 7,468) of liquid specimens with detectable ctDNA. The median age of patients with MEx14 alterations was 75 years, with 85% being ≥ 65 years, compared with a median age of 67 years in patients with NSCLC wild type (WT) for MEx14 alterations (P < .0001; Table 1). Subanalysis comparing MEx14 patients age ≥ 65 and < 65 years did not reveal any significant differences among sex, disease histology, or genomic characteristics (Appendix Table A1).

The majority of events classified as MEx14 alterations and included in this analysis are also included in the capmatinib CDx label (Appendix Fig A1, Appendix Table A2, category A, n = 1,508). However, additional variants expected to have the same functional effect but not included (eg, Y1003 CBL binding mutation or whole MEx14 deletion) or observed (eg, certain rare MEx14 splice variants) in the GEOMETRY trial, and therefore not covered under the CDx label, were also included in this study (category B, n = 91). MEx short variant alterations (point mutations or indels) outside MEx14 or within MEx14 but with unresolved functional implications were excluded from this analysis (category C, n = 194). Variants of unknown significance (category D, n = 2,206) were also excluded. Overall, alterations approved under the current capmatinib CDx label represent 94% (1, n = 2,206) were also excluded. Overall, alterations approved under the current capmatinib CDx label represent 94% (1, n = 1,508). However, additional variants expected to have the same functional effect but not included (eg, Y1003 CBL binding mutation or whole MEx14 deletion) or observed (eg, certain rare MEx14 splice variants) in the GEOMETRY trial, and therefore not covered under the CDx label, were also included in this study (category B, n = 91). MEx short variant alterations (point mutations or indels) outside MEx14 or within MEx14 but with unresolved functional implications were excluded from this analysis (category C, n = 194). Variants of unknown significance (category D, n = 2,206) were also excluded. Overall, alterations approved under the current capmatinib CDx label represent 94% (1, n = 1,508) of alterations predicted to activate MET through disruption of exon 14, and more generally, 84% (1, n = 1,793) of all MEx alterations with known or suspected oncogenic potential.

MEx14 alterations were observed across exon 14 splice functional sites: donor (31%), D1010 (22%), poly-pyrimidine tract (PPT, 17%), multiple 5’ sites (13%), multiple 3’ sites (12%), acceptor (2.3%), at Y1003 (2.3%), and whole exon deletions (0.44%). Alterations at the donor and acceptor sites were primarily base substitutions (94% and 75%), whereas indels were more likely to occur within the PPT and multiple functional sites at the 3’ or 5’ ends of exon 14. Similar rates of detection were observed in tissue and liquid cohorts (Fig 1). Median TMB of MEx14-altered NSCLC tumor samples was 3.8 mutations per megabase (muts per Mb) compared with 7.0 muts per Mb for NSCLC WT for MEx14 alterations (P < .001; Fig 2A). PD-L1 expression was available for 394 (25%) MEx14-altered and 16,909 (25%) MEx14 WT NSCLC tumor specimens. Of these, 84% MEx14-altered had a tumor proportion score (TPS) of > 1% compared with 59% of WT specimens (P < .001). Notably, the fraction of cases with low positive (1%-49%) TPS was relatively similar between WT and MEx14 cohorts (29% v 23%; P = .08), whereas high positive (≥ 50%) was significantly enriched in the MEx14-altered subset (30% v 60%; P < .001; Fig 2B). Neither median TMB nor PD-L1 expression significantly differed across alteration functional sites.

The most frequent coalterations in MEx14-altered tissue specimens were TP53 alterations (42%) and MDM2 amplification (34%); co-occurring CDK4 and MET amplifications were observed in 19% and 11% of cases (Fig 3A). MDM2 amplification and TP53 alterations were largely mutually exclusive, co-occurring in just 2.7% of cases. MDM2 and CDK4, both on chromosome 12q, were coamplified in 17% of MEx14-altered specimens; 90% of CDK4-amplified MEx14-altered specimens had MDM2 coamplification.

In MEx14-altered NSCLC ctDNA samples, co-occurrence patterns were generally similar to tissue for genes and alterations baited across both assays; however, MDM2 amplification was less commonly detected in liquid specimens (P < .001). MET coamplification was also significantly less common in liquid versus tissue MEx14-altered cases (0.75% v 11%; P = .0004; Appendix Fig A2).

Assessing all MEx14-altered samples, KRAS mutations occurred in 46 (2.9%), including 13% G12C, 52% other changes at codon G12, 20% changes at codon G13, and 15% other. Activating EGFR and ERBB2 mutations co-occurred in nine (0.57%) and five (0.31%) samples, respectively. Two samples harbored RET intron 11 rearrangements, and one harbored a CD74-ROS1 fusion (Appendix Table A3). Overall, codriver alterations were enriched in ctDNA (7.5%, 10 of 134) versus tissue (3.6%, 52 of 1,458; P = .03), and the presence of a second driver may represent acquired resistance (AR) in a subset of cases. Concurrent BRAFV600E, ALK, and NTRK fusions were not observed.

Samples from the same patient collected ≥ 60 days apart (median 372 days, range 144-1,603) with a MEx14 alteration in the primary sample were available for 43 patients including tissue-tissue (n = 29), tissue-ctDNA (n = 9), ctDNA-tissue (n = 1), and ctDNA-ctDNA pairs (n = 4). In total, 42 of 43 patients (98%) retained the primary MEx14 alteration, and 22 of 43 patients (51%) had reportable acquired alteration(s) detected. At least one secondary MEX mutation (Y1230C/H, D1228A/E/N/H, L1195V, and Y1003F) was acquired in nine specimens, with three specimens (one tissue and two ctDNA) acquiring ≥ 2 MEx mutations. Four samples had acquired MEx amplification (7-13 copies). Other acquired alterations included known oncogenic alterations in EGFR, ERBB2, KRAS, and AKT2 as well as alterations in other genes with likely significance in cancer, but with unestablished roles in AR. Acquired alterations, including secondary MEx mutations, were observed across MEx14 alteration subtypes. Although treatment history was not available for most cases, eight patients with multiple samples were confirmed to have had interim treatment with crizotinib or capmatinib (Fig 3B).

Fourteen patients with MEx14-alterations had both tissues and ctDNA samples available for concordance analysis (median 353 days between specimen collection, range 1-979; Appendix Table A4). Positive percent agreement with
### TABLE 1. Clinical and Molecular Characteristics of Patients With NSCLC Harboring MEtx14 Alterations by Functional Site

| Characteristics | MEtx14 WT NSCLC Patients | All MEtx14 Patients | PPT | Acceptor | Alters Multiple 5’ Sites | Y1003 | D1010 | Donor | Alters Multiple 3’ sites | Whole Exon Deletion |
|-----------------|--------------------------|---------------------|-----|----------|--------------------------|-------|-------|-------|--------------------------|-------------------|
| **Total cases** | 67,627                   | 1,592               | 276 | 36       | 208                      | 36    | 353   | 496   | 187                      | 7                 |
| **Tissue cases, % (n)** | 87 (58,786)               | 92 (1,458)          | 91 (251) | 92 (33) | 94 (196) | 100 (36) | 91 (322) | 91 (449) | 91 (170) | 100 (7) |
| **ctDNA cases, % (n)** | 13 (8,841)                | 8.4 (134)           | 9.1 (25) | 8.3 (3) | 5.8 (12) | 0.0 (0) | 8.8 (31) | 9.5 (47) | 9.1 (17) | 0.0 (0) |
| **Sex (M:F), %** | 50:50                    | 44:56               | 49:51 | 56:44   | 45:55 | 44:55 | 43:57 | 40:60 | 44:56 | 43:57 |
| **Median age, years, % (n)** | 67                       | 75                  | 76   | 78       | 75   | 76   | 75   | 73    | 73     | 79    |
| **< 65** | 42 (28,260) | 15 (236) | 16 (45) | 11 (4) | 17 (35) | 14 (5) | 12 (42) | 16 (78) | 15 (28) | 0.0 (0) |
| **≥ 65** | 58 (39,191) | 85 (1,351) | 84 (230) | 89 (32) | 83 (173) | 86 (31) | 88 (311) | 83 (449) | 85 (159) | 100 (7) |
| **Genomic ancestry, % (n)** | European 78 (45,527) | 79 (1,138) | 76 (190) | 81 (26) | 76 (148) | 75 (27) | 79 (252) | 81 (360) | 80 (135) | 43 (3) |
| **African** | 8.9 (5,229) | 5.7 (77) | 5.6 (14) | 0.0 | 6.1 (12) | 5.6 (2) | 5.6 (18) | 4.7 (21) | 4.7 (8) | 29 (2) |
| **Admixed American** | 6.7 (3,930) | 8.3 (120) | 10 (25) | 9.4 (3) | 12 (24) | 8.3 (3) | 8.4 (27) | 6.1 (27) | 5.9 (10) | 29 (2) |
| **East Asian** | 5.7 (3,368) | 7.1 (103) | 7.6 (19) | 9.4 (3) | 5.6 (11) | 8.3 (3) | 6.6 (21) | 7.4 (33) | 8.9 (15) | 0.0 (0) |
| **South Asian** | 1.0 (592) | 0.55 (8) | 0.40 (1) | 0.0 | 0.51 (1) | 2.8 (1) | 0.63 (2) | 0.45 (2) | 0.59 (1) | 0.0 (0) |
| **PD-L1-positive (> 1%), % (n)** | 59 (9,978/16,909) | 84 (329/394) | 81 (5669) | 88 (78) | 87 (40/46) | 91 (10/11) | 84 (80/95) | 87 (99/114) | 73 (37/51) | 100 (1/1) |
| **Median TMB (muts per Mb)** | 7.0 | 3.8 | 4.8 | 6.1 | 3.5 | 3.8 | 3.8 | 3.5 | 2.6 | 4.8 |
| **TMB > 20, % (n)** | 12 (6,668/57,922) | 1.2 (18/1,454) | 2.4 (6/248) | 9.1 (3/33) | 0.0 (0/196) | 2.8 (1/36) | 0.62 (2/322) | 0.67 (3/448) | 1.8 (3/170) | 0.0 (0/7) |
| **TMB 15-20, % (n)** | 7.8 (4,543/57,922) | 1.9 (27/1,454) | 2.0 (5/248) | 0.0 (0) | 1.0 (2/196) | 8.3 (3/36) | 1.6 (5/322) | 2.0 (9/448) | 1.2 (2/170) | 14 (1/7) |
| **TMB 5-15, % (n)** | 44 (25,543/57,922) | 37 (539/1,454) | 43 (106/248) | 42 (14/33) | 39 (77/196) | 22 (8/36) | 40 (130/322) | 35 (159/448) | 27 (46/170) | 29 (2/7) |
| **TMB < 5, % (n)** | 37 (21,168/57,922) | 60 (870/1,454) | 53 (131/248) | 48 (16/33) | 60 (117/196) | 67 (24/36) | 57 (185/322) | 62 (277/448) | 70 (119/170) | 57 (4/7) |
| **Tobacco signature, % (n)** | 27 (6,909/25,596) | 7.3 (24/330) | 9.4 (6/64) | 20 (2/10) | 0.0 (0/38) | 14 (1/7) | 6.1 (5/82) | 6.5 (6/93) | 11 (4/36) | 0.0 (0/2) |
| **Histologic subtype, % (n)** | Adenocarcinoma 63 (42,815) | 65 (1,032) | 66 (183) | 78 (28) | 64 (134) | 75 (27) | 64 (226) | 64 (318) | 63 (117) | 71 (5) |
| **Adenosquamous** | 0.67 (455) | 2.6 (42) | 2.5 (7) | 0.0 (0) | 5.3 (11) | 0.0 (0) | 1.7 (6) | 2.4 (12) | 3.2 (6) | 0.0 (0) |
| **Squamous** | 16 (10,504) | 9.9 (158) | 8.0 (22) | 8.3 (3) | 9.1 (19) | 14 (5) | 12 (41) | 9.7 (48) | 11 (20) | 0.0 (0) |
| **Large cell** | 1.9 (1,258) | 0.38 (6) | 0.36 (1) | 0.0 (0) | 0.0 (0) | 0.0 (0) | 0.28 (1) | 0.40 (2) | 1.1 (2) | 0.0 (0) |
| **Sarcomatoid** | 0.69 (469) | 3.5 (55) | 4.7 (13) | 8.3 (3) | 1.9 (4) | 0.0 (0) | 3.1 (11) | 3.4 (17) | 3.7 (7) | 0.0 (0) |
| **NSCLC NOS** | 18 (12,120) | 19 (299) | 18 (50) | 5.6 (2) | 19 (40) | 11 (4) | 19 (68) | 20 (99) | 19 (35) | 29 (2) |
| **Concurrent MDM2 amp** | 3.4 (2,318) | 31 (499) | 36 (98) | 25 (9) | 34 (70) | 28 (10) | 28 (100) | 32 (157) | 29 (55) | 43 (3) |

(Continued on following page)
| Characteristics     | METex14 WT NSCLC Patients | All METex14 Patients | PPT | Acceptor | Alters Multiple 5’ Sites | Y1003 | D1010 | Donor | Alters Multiple 3’ sites | Whole Exon Deletion |
|---------------------|---------------------------|----------------------|-----|----------|--------------------------|-------|-------|-------|--------------------------|---------------------|
| Concurrent CDK4 amp  | 2.6 (1,753)               | 18 (281)             | 22 (61) | 17 (6)   | 18 (38)                  | 19 (7) | 16 (55) | 18 (87) | 15 (28)                  | 0.0 (0)             |
| Concurrent MET amp   | 2.4 (1,637)               | 10 (163)             | 11 (29) | 14 (5)   | 11 (22)                  | 8.3 (3) | 8.5 (30) | 13 (63) | 5.9 (11)                  | 14 (1)              |
| KRAS mutation        | 27 (18,510)               | 2.9 (46)             | 2.2 (6) | 5.6 (2)  | 3.4 (7)                  | 2.8 (1) | 4.0 (14) | 2.8 (14) | 1.1 (2)                   | 0.0 (0)             |
| EGFR mutation*      | 13 (8,689)                | 0.57 (9)             | 0.72 (2) | 2.8 (1)  | 0.48 (1)                 | 2.8 (1) | 0.0 (0)  | 0.40 (2) | 1.1 (2)                   | 0.0 (0)             |
| ERBB2 mutation      | 2.2 (1,472)               | 0.31 (5)             | 0.36 (1) | 0.0 (0)  | 0.0 (0)                  | 0.0 (0) | 0.0 (0)  | 0.0 (0)  | 0.53 (1)                  | 0.0 (0)             |
| RET rearrangement   | 1.1 (741)                 | 0.13 (2)             | 0.0 (0) | 0.0 (0)  | 0.0 (0)                  | 0.0 (0) | 0.0 (0)  | 0.0 (0)  | 0.0 (0)                   | 0.0 (0)             |
| ROS1 rearrangement  | 0.78 (529)                | 0.06 (1)             | 0.0 (0) | 0.0 (0)  | 0.0 (0)                  | 0.0 (0) | 0.28 (1) | 0.0 (0)  | 0.0 (0)                   | 0.0 (0)             |

Abbreviations: amp, amplification; ctDNA, circulating tumor DNA; NOS, not otherwise specified; NSCLC, non–small-cell lung cancer; PPT, polypyrimidine tract; TMB, tumor mutational burden; WT, wild type.

*Only a subset of samples had genetic ancestry predictions available.

bOnly a subset of samples had PD-L1 immunohistochemistry results available.

cOnly a subset of tissue samples had TMB reported.

dOnly a subset of samples had tobacco signature calls.

eLimited to EGFR known driver mutations (exon 19 deletion or insertion, L858R, G719X, S768I, L861Q) and ERBB2 exon 20 insertions (n = 0) or S310X mutation (n = 2; Appendix Table A4).
the tissue biopsy was 92% over all pairs and 100% for pairs collected within 1 year. In 2 of 14 discordant pairs (14%), one lacked METex14 alteration in a ctDNA specimen with a low estimated composite tumor fraction (0.62%), and in the other, the primary tissue specimen harbored EGFR L858R while the ctDNA specimen collected post-afatinib treatment harbored multiple heterogenous AR mechanisms including a METex14 skipping alteration.

**Cases With Multiple METex14 Alterations**

Among 1,592 METex14-altered NSCLC samples, nine samples (eight tissue samples and one ctDNA sample) harbored multiple METex14 alterations (Appendix Table A5). In five cases, on the basis of proximity, the alterations were able to be assessed for cis and trans status and two were in cis and three were in trans. In one case, a single METex14 alteration (43% variant allele frequency [VAF]) was detected in a primary lung sample, and then a second lung biopsy collected 286 days later revealed the initial donor site alteration (3% VAF) and acquired MET Y1003F (31% VAF) in trans.

**CGDB Treatment Patterns and Outcomes Analysis**

Of 6,439 patients with advanced NSCLC in the CGDB meeting criteria for assessment, METex14 alterations were detected in 148 (2.3%) cases (Appendix Fig A3). Clinical characteristics, genomic characteristics, and therapeutic regimens are listed in Table 2. Fifty-three patients began first-line therapy before the CGP report: 24 (45%) on an IO-containing regimen without MET TKI, 13 (25%) on the chemotherapy-containing regimen without IO or MET TKI, 11 (21%) on MET TKI (crizotinib or cabozantinib)-containing regimen, and five (9.4%) with an unspecified clinical study drug that may have included a MET TKI (Fig 4A). For comparison, 61 patients began first-line therapy before the CGP report: 35 (57%) on the chemo-containing regimen, 20 (33%) on the IO-containing regimen, three (4.9%) on the MET TKI-regimen, two (3.3%) on erlotinib (EGFR TKI), and one (1.6%) on an unspecified clinical study drug (Fig 4A). For the three patients who started MET TKI before CGP, therapy was initiated less than a month before the report, so we suspect that a preliminary report may have influenced the treatment decision. Similar patterns were observed for second-line therapy pre- and post-CGP reports. Of patients who received a MET TKI first-line post-CGP report, five of 11 patients (45%) went on to receive second-line therapy; however, four of 11 patients remained on first-line therapy at the time of analysis (Fig 4B). Overall, 42 of 148 METex14 patients had documented receipt of MET TKI post-CGP biopsy (primarily crizotinib monotherapy) at some point during their treatment history, distributed across first-seventh lines. For 31 patients with available data, the real-world response (rWR) rate was 45% (2 complete response and 12 partial response) and median time to therapy discontinuation (TTD) on MET TKI was 4.4 months, with seven patients still on therapy at the time of analysis (Fig 4C, Appendix Table A6).

**DISCUSSION**

We assessed the largest cohort to date of 1,592 METex14-altered NSCLC samples. The METex14 alteration frequency observed here (2.3%) is similar to previously published studies and shows a diverse spectrum of alterations. The large size of this landmark analysis allowed for high-

---

**FIG 1.** Distribution of MET exon 14 alterations by functional site and event type. Functional site categories are shown on the x-axis aligned with the corresponding schematic showing exon 14 and flanking introns. Colored bars indicate METex14 alteration type. Deletion events (including short variants and rearrangements) resulting in complete deletion of exon 14 are indicated in orange. Left bars: METex14 events detected in tissue. Right bars: METex14 events detected in liquid. PPT, pyrimidine tract.
resolution confirmation of frequencies of coalterations and IO biomarkers reported in previous smaller studies. We identified rare cases with co-occurring drivers, including 1.9% with KRAS mutations at G12, which may represent AR. In available paired cases, a subset of whom had documented interim treatment with crizotinib or capmatinib, the majority had reportable acquired alterations detected, including secondary MET resistance mutations, MET amplification, and alterations in EGFR, ERBB2, KRAS, and the PI3K pathway, as well as other acquired alterations potentially relevant in cancer but not previously described as AR mechanisms to MET inhibitors.13-16 In 49% of paired cases, no acquired alterations were reported, suggesting either a yet to be identified mechanism driving resistance, an AR mechanism present but below the limit of detection, or that the second sample may not have been collected at the point of AR to MET inhibition. Interestingly, identification of acquired alterations was less common when the samples were collected > 2 years apart. Multiple heterogenous AR mechanisms were observed in both tissue and liquid samples and were not more frequent in ctDNA in our cohort of paired samples, although in non-paired samples, codrivers were more commonly detected with METex14 in ctDNA vs tissue. Cases with multiple drivers may be sensitive to combination treatment with approved and investigational therapies now available targeting receptor tyrosine kinases and KRASG12C in NSCLC.

Assessment of IO biomarkers confirmed that PD-L1 expression is elevated in METex14-altered samples; however, clinical data have suggested that despite elevated PD-L1 expression, patients with METex14-altered NSCLC have low response rates to IO and responses are not correlated with PD-L1 expression, which is consistent with low median TMB observed in METex14-altered samples.17,19 METex14 skipping alterations are currently the only MET alterations associated with FDA-approved therapies and a companion diagnostic in NSCLC.11 However, METex14

FIG 2. Tumor mutational burden and PD-L1 expression across METex14 alteration subtypes. (A) Distribution and median TMB (muts per Mb) and (B) PD-L1 expression by immunohistochemistry by METex14 functional site compared with NSCLC WT for METex14 alterations. PD-L1 expression was reported using the TPS: negative if the percentage of tumor cells staining with ≥ 1 + intensity was < 1%, low positive if 1%-49%, or high positive if ≥ 50%. mut, mutations; NSCLC, non–small-cell lung cancer; PD-L1, XXX; PPT, polypyrimidine tract; TMB, tumor mutational burden; TPS, tumor proportion score; WT, wild type.
FIG 3. Co-occurring alterations in NSCLC tissue samples positive for METex14 alterations. (A) Oncoprint of co-occurring alterations in > 5% of cases. (B) Potential acquired resistance alterations in 44 paired samples. Acquired alterations are listed at the top of each bar, and bars are color coded by the category of acquired alteration. *Indicates that second paired sample was liquid biopsy. Original METex14 alteration was not detected in the second sample; in one of these cases, a different METex14 alteration was acquired, but similar coalterations were observed between samples; in the other case, an EGFRex19ins was acquired post-crizotinib with different somatic coalterations suggesting potential detection of DNA from a second primary tumor in the lymph node biopsy. **Genes included on 11q13 amp include CCND1, FGF19, FGF3, and FGF4. Genes on 19q amp include CCNE1, AKT2, and AXL. Genes on 14q amp include BCL2L2, NFKBIA, and NKO2-1. amp, amplification; cap, known interim treatment with capmatinib; CN, copy number alteration; criz, known interim treatment with crizotinib; del, homozygous deletion; ins, insertion; NSCLC, non–small-cell lung cancer; RE, gene rearrangement; RTK, receptor tyrosine kinase; SV, short variant mutation.
skipping alterations that are on-label for capmatinib represent 84% (Appendix Fig A1) of MET short variant alterations with known or suspected oncogenic potential in the FMI database, and 94% of MET ex14 variants predicted to result in activation through disruption of exon 14 or CBL binding. It is worth noting that mutations surrounding the CBL binding site at positions D1002 and R1004-E1009 may affect CBL binding and confer sensitivity to MET TKIs similar to Y1003 mutation; however, these alterations are still relatively uncharacterized and thus excluded from primary analysis in this study. Ultimately, variation in how MET ex14 biomarkers are defined may lead to confusion in terms of actionability, highlighting the need for standardization.

Given the diversity of METex14 alterations, distinguishing accurate methods for detection can be challenging. A variety of DNA- and RNA-based methods are clinically available for METex14 alteration detection, but there is only one FDA-approved CDx. Some DNA-based platforms have incomplete coverage of regions where alteration is known to alter METex14 skipping, such as the splice acceptor site, so critical assessment of available diagnostics is essential for comprehensive detection. RNA profiling is also an emerging methodology to detect exclusion of exon 14 from the mRNA. In rare cases, RNA profiling may detect variants not detected via DNA sequencing; however, the FoundationOne CDx DNA assay was shown in the GEOMETRY trial to be highly concordant with RNA sequencing methods.

Table 2. Treatment Patterns and Clinicogenomic Characteristics of Patients With NSCLC Harboring METex14 Alterations’ Patients in the FMI-FH CGDB

| Characteristics | METex14 Cases |
|-----------------|---------------|
| Total tissue cases, n | 148 |
| Sex (M:F), % | 45:55 |
| Median age at advanced diagnosis, years | 75 |
| Stage at diagnosis, % (n) |
| I | 9.5 (14) |
| II | 4.7 (7) |
| III | 24 (36) |
| IV | 59 (87) |
| Unknown | 2.7 (4) |
| Practice type, % (n) |
| Academic | 6.8 (10) |
| Community | 93 (138) |
| Genomic ancestry, % (n)* |
| European | 85 (125) |
| African | 6.1 (9) |
| East Asian | 5.4 (8) |
| Admixed American | 3.4 (5) |
| South Asian | 0 (0) |
| METex14 alteration functional site, % (n) |
| Polypurine tract | 18 (27) |
| Acceptor | 3.4 (5) |
| Alters multiple 5’ sites | 11 (16) |
| Y1003 | 4.7 (7) |
| D1010 | 20 (30) |
| Donor | 33 (49) |
| Alters multiple 3’ sites | 8.8 (13) |
| Multiple METex14 alterations | 0.68 (1) |
| Smoking status, % (n) |
| History of smoking | 65 (96) |
| No history of smoking | 35 (52) |
| Histologic subtype, % (n) |
| Nonsquamous | 85 (126) |
| Squamous | 10 (15) |
| NSCLC NOS | 4.7 (7) |
| PD-L1 IHC status, % (n)** |
| High positive (≥ 50%) | 61 (27/44) |
| Low positive (1%-49%) | 25 (11/44) |
| Negative | 14 (6/44) |
| Median TMB, muts per Mb | 4.3 |
| Therapy documented after CGP report, % (n)** | 61 (90) |
| First therapy documented after CGP report, % (n) | 33 (30) |

*Only a subset of samples had an ancestry prediction available.
**Only a subset of samples had PD-L1 IHC results available.
*No therapy postreceipt of CGP report was documented in the CGDB for 58 of 148 METex14 patients.
Excludes METi + IO combination.
Excludes chemo + IO and chemo + METi.

Abbreviations: CGDB, clinicogenomic database; CGP, comprehensive genomic profiling; FH, Flatiron Health; FMI, Foundation Medicine; IHC, immunohistochemistry; IO, immunotherapy; METi, MET inhibitors; NOS, not otherwise specified; NSCLC, non–small-cell lung cancer; PD-L1, XXX; TMB, tumor mutational burden.

Lee et al

1362 © 2021 by American Society of Clinical Oncology
FIG 4. Real-world treatment patterns of patients with METex14-altered NSCLC in the CGDB. (A) Distribution of 1L and 2L therapies before and after CGP for 114 METex14-altered NSCLC who started treatment after CGP biopsy. All patients captured started 1L therapy between 2012 and 2020. (B) Sankey diagram of 53 patients with METex14-altered NSCLC with documented receipt of 1L therapy in the CGDB after report of CGP results. All patients captured started 1L therapy post-CGP report between 2015 and 2020. Categorical groupings include (1) METi-containing regimen: MET TKI monotherapy, MET TKI + chemotherapy, and MET TKI + IO, (2) IO-containing regimen: IO monotherapy, IO + chemotherapy, IO + clinical study drug, or IO + other targeted therapy, (3) chemo-containing regimen: chemotherapy monotherapy, chemotherapy + clinical study drug, or chemotherapy + other targeted therapy, and (4) other: non-MET targeted therapy (erlotinib, aflatinib, ceritiniib, or bevacizumab) or unspecified clinical study drug, which may have included a MET TKI. Six patients who received MET TKI in the fourth to seventh lines are not captured here but are shown in (C). (C) Swimmer plot displaying time to treatment discontinuation for patients with METex14-altered NSCLC who received MET TKI. rwR was available for a subset of patients. 1L, first line; 2L, second line; CGP, comprehensive genomic profiling; CR, complete response; IO, immunotherapy; NSCLC, non–small-cell lung cancer; METi, MET inhibitors; PD, progressive disease; PR, partial response; rwR, real-world response; SD, stable disease; TKI, tyrosine kinase inhibitor.
Comparing tissue and liquid cohorts, METex14 alterations were less commonly detected in ctDNA, which may be due in part to practice testing patterns. We also saw decreased frequency of coamplifications in the ctDNA cohort, which is generally known regarding amplification detection in ctDNA, and should be taken into consideration as the functional and therapeutic significance of these coamplifications is further elucidated. In a small cohort of 14 cases with tissue and liquid samples collected from the same patient, concordance was high for METex14 detection (100% positive percent agreement for samples collected 1 year apart). In the VISION trial, similar outcomes to tepotinib were reported for cases with METex14 alterations detected in tissue or ctDNA, further supporting the utility of either method for detecting these alterations.

In very rare cases, we saw multiple distinct METex14 skipping alterations in the same tissue (n = 8) or ctDNA (n = 1) sample. Both cis and trans relationships between the two METex14 events were observed, and VAF relationships for METex14 events were also variable. Unfortunately, clinical histories were not available for most of these cases, and it remains unclear whether these cases typically represent multiple primaries, AR, or another phenomenon. However, in a separate NSCLC case, two tissue samples determined to have been collected from multiple primary tumors in the same patient each harbored a distinct METex14 alteration (Mark Awad, ASCO 2020 Oral Presentation).

Using the CGDB, we observed higher MET inhibitor usage post-CGP report compared with before CGP was performed (39% v 4.9%), although off-label use of MET inhibitors was still a minority presumably due to lack of physician confidence in crizotinib efficacy, barriers to access, or preference for IO on the basis of positive PD-L1 staining. We plan to investigate timing of receipt of PD-L1 IHC results and METex14 CGP results, and potential impact on therapy selection in follow-up studies. Compared with results reported for the PROFILE 1001 trial, the rwR rate of 45% seen here was somewhat higher than the 32% ORR reported, although limitations to interpretation of rwR are noted below. Conversely, PFS was not available in the CGDB, but the median TTD of 4.4 months seen here was shorter than the 7.3 month median PFS reported on trial. This could be due to a number of reasons including (1) for our TTD analysis, seven patients still remained on MET TKI at the time of data cutoff, (2) patients treated in the RW setting likely had worse performance status on average, and (3) differences between TTD and PFS as noted below.

Limitations of this study include lack of clinical history and treatment information for most patients in the FMI genomic database. For the CGDB cohort, clinical data were derived

![FIG 4. (Continued).](image-url)
from EHR and data not documented in the EHR may be incomplete or missing, particularly for events occurring outside of the FH network. In particular, rWR and TTD were retrospectively captured from EHR, which differs from prospective collection of progression data within the context of a clinical trial. TTD is also used as a proxy for PFS, and patients may have discontinued drug for reasons other than disease progression. Furthermore, all patients in this study received CGP, which may introduce selection bias for patients treated by physicians with distinct practice patterns. Data were collected over a period where the MET inhibitor treatment landscape was rapidly evolving, and outcomes data are biased toward off-label crizotinib, which was available before newer specific MET inhibitors were developed.

Overall, we assessed available characteristics for more than 1,500 METex14-altered NSCLC cases, including the landscape of coalterations that may modulate response to targeted and immunotherapies. We also compared genomics of tissue and liquid cohorts and observed high concordance for METex14 alterations, although coalterations may be better assessed in tissue. These data and continued use of CGP to characterize this patient population will be useful to predict response to MET inhibitors and may be imperative for the selection of effective combination therapies.

**AFFILIATIONS**

1. Foundation Medicine Inc, Cambridge, MA
2. Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA

**CORRESPONDING AUTHOR**

Alexa B. Schrock, PhD, Foundation Medicine Inc, 150 Second St, Cambridge, MA 02141; e-mail: aschrock@foundationmedicine.com.

**PRIOR PRESENTATION**

Presented in part at ASCO 2020 oral presentation (Awad et al, abstr 9511).

**AUTHOR CONTRIBUTIONS**

Conception and design: Jessica K. Lee, Garrett M. Frampton, Alexa B. Schrock
Financial support: Brian M. Alexander
Administrative support: Brian M. Alexander
Collection and assembly of data: Garrett M. Frampton, Alexa B. Schrock
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

The following represents disclosure information provided by the authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/doi/10.1200/JCO.18.00713-abstract.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Jessica K. Lee
Employment: Foundation Medicine
Stock and Other Ownership Interests: Roche

Russell Madison
Employment: Foundation Medicine
Stock and Other Ownership Interests: Roche

Anthony Classon
Employment: Foundation Medicine
Stock and Other Ownership Interests: Roche

Ole Gjoerup
Employment: Foundation Medicine
Stock and Other Ownership Interests: Roche

Mark Rosenzweig
Employment: Foundation Medicine
Stock and Other Ownership Interests: Foundation Medicine

Garrett M. Frampton
Employment: Foundation Medicine
Stock and Other Ownership Interests: Roche

Brian M. Alexander
Employment: Foundation Medicine
Leadership: Foundation Medicine
Stock and Other Ownership Interests: Roche
Research Funding: Lilly, Puma Biotechnology, Celgene
Open Payments Link: https://openpaymentsdata.cms.gov/physician/894258/summary

Geoffrey R. Oxnard
Employment: Foundation Medicine
Stock and Other Ownership Interests: Roche

Jeffrey M. Venstrom
Employment: Foundation Medicine, Genentech/Roche
Leadership: Foundation Medicine
Stock and Other Ownership Interests: Roche
Consulting or Advisory Role: Synkino Biotherapeutics
Travel, Accommodations, Expenses: Foundation Medicine, Genentech/Roche

Mark M. Awad
Consulting or Advisory Role: Genentech, Merck, Pfizer, Boehringer Ingelheim, AbbVie, AstraZeneca/MedImmune, Clovis Oncology, Nektar, Bristol Myers Squibb, ARIAD, Foundation Medicine, Syndax, Novartis, Blueprint Medicines, Maverick Therapeutics, Achilles Therapeutics, Neon Therapeutics, Hengrui Therapeutics, Gritstone Oncology, Archer, Mirati Therapeutics, NextCure, EMD Serono, AstraZeneca, Panasonic, Instil Bio

**DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/doi/10.1200/JCO.18.00713-abstract.
REFERENCES

1. Schrock AB, Frampton GM, Suh J, et al: Characterization of 298 patients with lung cancer harboring MET Exon 14 skipping alterations. J Thorac Oncol 11:1493-1502, 2016

2. Frampton GM, Ali SM, Rosenzweig M, et al: Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. Cancer Discov 5:850-860, 2015

3. Awad MM, Oxnard GR, Jackman DM, et al: MET exon 14 mutations in non-small-cell lung cancer are associated with advanced age and stage-dependent MET genomic amplification and c-Met overexpression. J Clin Oncol 34:721-730, 2016

4. Kong-Beltran M, Seshagiri S, Zha J, et al: Somatic mutations lead to an oncogenic deletion of Met in lung cancer. Cancer Res 66:283-289, 2006

5. Onozato R, Koka T, Kuwano H, et al: Activation of MET by gene amplification or by splice mutations deleting the juxtamembrane domain in primary resected lung cancers. J Thorac Oncol 4:5-11, 2008

6. Comoglio PM, Trusolino L, Boccaccio C: Known and novel roles of the MET oncogene in cancer: A coherent approach to targeted therapy. Nat Rev Cancer 18:341-358, 2018

7. Peschard P, Fournier TM, Lamorte L, et al: Mutation of the c-Cbl TKB domain binding site on the Met receptor tyrosine kinase converts it into a transforming protein. Mol Cell 8:995-1004, 2001

8. van der Steen N, Giovannetti E, Pauwels P, et al: MET exon 14 skipping: From the structure to the clinic. J Thorac Oncol 11:1423-1432, 2016

9. Driben A, Clark JW, Weiss J, et al: Antitumor activity of crizotinib in lung cancers harboring a MET exon 14 alteration. Nat Med 26:47-51, 2020

10. Lu S, Fang J, Cao L, et al: Preliminary efficacy and safety results of savolitinib treating patients with pulmonary sarcomatoid carcinoma (PSC) and other types of non-small cell lung cancer (NSCLC) harboring MET exon 14 skipping mutations. Cancer Res 79, 2019 (abstr CT031)

11. Wolf J, Seto T, Han JY, et al: Capmatinib in MET exon 14-mutated or MET-amplified non-small-cell lung cancer. N Engl J Med 383:944-957, 2020

12. Iwamoto F, Haghani H, Bardia A, et al: MET-directed therapies for non-small cell lung cancer. J Thorac Oncol 12:1221-1232, 2017

13. Sabari JK, Leonardi GC, Shu CA, et al: PD-L1 expression, tumor mutational burden, and response to immunotherapy in patients with MET exon 14 altered lung cancers. Ann Oncol 29:2085-2091, 2018

14. Birnbaum B, Nussbaum N, Seidl-Rathkopf K, et al: Model-assisted cohort selection with bias analysis for generating large-scale cohorts from the EHR for oncology research. 2020. http://lanef.org/abs/2001.09765

15. Callies A, Riess JW, Brahmer JR: Checkpoint blockade in lung cancer with driver mutation: Choose the road wisely. Am Soc Clin Oncol Ed Book 40:372-384, 2020

16. Miao YL, Xu QQ: MET Y1003S point mutation shows sensitivity to crizotinib in a patient with lung adenocarcinoma. Lung Cancer 130:84-86, 2019

17. Calles A, Riess JW, Brahmer JR: Checkpoint blockade in lung cancer with driver mutation: Choose the road wisely. Am Soc Clin Oncol Ed Book 40:372-384, 2020

18. Calles A, Riess JW, Brahmer JR: Checkpoint blockade in lung cancer with driver mutation: Choose the road wisely. Am Soc Clin Oncol Ed Book 40:372-384, 2020

19. Newberg J, Connelly C, Frampton G: Determining patient ancestry based on targeted tumor comprehensive genomic profiling. Cancer Res 79, 2019 (suppl; abstr 1599)
APPENDIX 1. SUPPLEMENTAL MATERIALS

Foundation Medicine Comprehensive Genomic Profiling

As previously described, for 60,244 tumor tissue specimens, DNA (≥ 50 ng) was extracted from formalin-fixed paraffin-embedded specimens and next-generation sequencing was performed by hybridization-captured, adapter ligation-based libraries to high, uniform coverage (≥ 500×) for all coding exons of 187-324 cancer-related genes plus selected introns. For 8,975 liquid samples, plasma was isolated from 20 mL of peripheral whole blood and ≥ 20 ng of circulating tumor DNA (ctDNA) was extracted to create adapted sequencing libraries for coding exons of 60 or 70 genes before hybrid capture and sample-multiplexed sequencing. Results were analyzed for base substitutions (subs), short insertions and deletions (indels), copy number gains or losses, and rearrangements; copy losses were not reported for liquid samples included in this study. For all assay versions, all coding exons of MET were baited, but there was no dedicated baiting of MET introns.

Tumor mutational burden was defined as the number of somatic mutations per megabase (mb) postfiltering to remove known somatic and deleterious mutations. The total number of mutations was divided by the coding region target territory of the assay to calculate the mutation burden per mb. PD-L1 expression was determined by immunohistochemistry performed on tissue sections using the 22C3 (Dako) PD-L1 antibody. PD-L1 expression was reported using the tumor proportion score (TPS), where TPS = No. of PD-L1-positive tumor cells/total No. of PD-L1-positive + PD-L1-negative tumor cells. The TPS result was stratified into negative (< 1%), low positive (1%-49%), and high positive (≥ 50%).

For liquid biopsy specimens, composite tumor fraction (cTF) was used to estimate the ctDNA fraction. cTF leverages two complementary methods, tumor fraction (TF) estimate and maximum somatic allele frequency (MSAF). When ctDNA fraction is higher, a TF estimate is calculated on the basis of a measure of tumor aneuploidy that incorporates observed deviations in coverage across the genome for a given sample. Calculated values for this metric are calibrated against a training set on the basis of samples with well-defined tumor fractions to generate an estimate of TF. When ctDNA content is lower, MSAF is determined by calculating the allele fraction for all known somatic, likely somatic, and variant of unknown significance base substitutions, excluding certain common and rare germline variants. The cTF is based on the TF estimate when available and is generated from MSAF when lack of tumor aneuploidy limits the ability to return an informative estimate of TF.

Genomic ancestry was determined for each individual. Single-nucleotide polymorphisms targeted by each of our comprehensive genomic profiling (CGP) tissue tests were superimposed with phase III 1000 genomes’ data. Using an established approach, we projected the single-nucleotide polymorphisms down to the top five principal components and used random forest ensemble learning to train a classifier on each profiling test. Classifiers were trained to recognize five general ancestries: African (AFR), admixed American (AMR), East Asian (EAS), European (EUR), and South Asian (SAS).

Flatiron Health-Foundation Medicine Clinicogenomic Database

Patients who were diagnosed with metastatic disease > 90 days before their first visit within the Flatiron Health (FH) network or who received their Foundation Medicine report > 60 days after their last FH visit date were excluded to ensure all therapies received before CGP were captured and to exclude patients who left the FH network before CGP. This left 6,439 unique patients eligible for this study. Clinical characteristics and treatment information were obtained via technology-enabled abstraction of clinical notes and radiology and pathology reports and linked to CGP data.

Statistical Analysis and Real-World End Points

The Fisher exact test was used to assess significance of categorical relationships, and the Kruskal-Wallis test was used to assess significance of continuous variables. False discovery rate correction was performed by the Benjamini-Hochberg procedure to correct P values for multiple tests.
FIG A2. Co-occurring alterations in \textit{MET}ex14-positive tissue and liquid specimens. Analysis is limited to genes and alterations baited across both assays. Genes altered in $>5\%$ of samples in either cohort are shown. Homozygous losses were not reported in the majority of liquid specimens and were excluded. Cases with multiple \textit{MET} alterations were primarily those with \textit{MET}ex14 skipping alteration and co-\textit{MET} amplification. $^*q < 0.05$; $^{**}q < 0.001$. CNA, copy number alteration; RE, rearrangement; SV, short variant.
FIG A3. Cohort selection and treatment patterns for patients with \textit{MET}ex14-altered NSCLC available for assessment in the CGDB: (A) cohort eligibility diagram and (B) treatment patterns diagram. *Of patients who received therapy postspecimen collection, 37 of 42 METi-treated, 24 of 75 platinum chemotreated, and 40 of 70 IO-treated patients began therapy post-CGP report receipt. CGDB, clinicogenomic database; CGP, comprehensive genomic profiling; FMI, Foundation Medicine; IO, immunotherapy; METi, MET inhibitors; NSCLC, non-small-cell lung cancer.
**TABLE A1.** Genomic Comparison Between Patients Age < 65 and ≥ 65 Years With MET<sup>ex14</sup>-Altered NSCLC

| Characteristics                          | < 65 Years | ≥ 65 Years | P   |
|------------------------------------------|------------|------------|-----|
| Total cases, n<sup>a</sup>               | 236        | 1,351      |     |
| Sex (M:F), %                             | 38:62      | 45:55      | .06 |
| MET<sup>ex14</sup> alteration functional site, % (n) |           |            |     |
| PPT                                      | 19 (45)    | 17 (230)   | .96 |
| Acceptor                                 | 1.7 (4)    | 2.4 (32)   | .96 |
| Alters multiple 5’                       | 15 (35)    | 13 (173)   | .96 |
| Y1003                                    | 2.1 (5)    | 2.3 (31)   | 1.0 |
| D1010                                    | 18 (42)    | 23 (311)   | .96 |
| Donor                                    | 33 (78)    | 31 (414)   | .96 |
| Alters multiple 3’                       | 12 (28)    | 12 (159)   | 1.0 |
| Whole exon deletion                      | 0.0 (0)    | 0.52 (7)   | .96 |
| Histology, % (n)                         |            |            |     |
| Adenocarcinoma                           | 62 (147)   | 65 (882)   | .96 |
| Adenosquamous                            | 2.5 (6)    | 2.7 (36)   | 1.0 |
| Squamous                                 | 9.7 (23)   | 10 (135)   | 1.0 |
| Large cell                               | 0.0 (0)    | 0.44 (6)   | .96 |
| Sarcomatoid                              | 4.7 (11)   | 3.3 (44)   | .96 |
| NSCLC NOS                                | 21 (49)    | 18 (248)   | .96 |
| Median TMB (muts per Mb)                 | 3.5        | 3.8        | .28 |
| PD-L1-positive (≥ 1%), % (n)<sup>b</sup> | 86 (42/49) | 83 (286/344)| 1.0 |
| Concurrent MDM2 amp                      | 35 (83)    | 30 (410)   | .96 |
| Concurrent CDK4 amp                      | 20 (48)    | 17 (231)   | .96 |
| Concurrent MET amp                       | 9.3 (22)   | 10 (139)   | 1.0 |

Abbreviations: amp, amplification; NOS, not otherwise specified; NSCLC, non–small-cell lung cancer; PPT, polypyrimidine tract; TMB, tumor mutational burden.

<sup>a</sup>Age was not available for five patients.

<sup>b</sup>Only a subset of samples had PD-L1 immunohistochemistry results available.
**TABLE A2.** Classification of All MET Alterations in the Foundation Medicine Genomic Database

| MET Alteration Category | MET Alteration | % of All MET Alterations (n) |
|-------------------------|----------------|-----------------------------|
| A: On label for Capmatinib METex14 CDx | Donor base sub | 12 (467) |
|                         | D1010 base sub | 8.6 (343) |
|                         | PPT deletion   | 6.4 (255) |
|                         | Multiple 5’ deletion | 5.2 (208) |
|                         | Multiple 3’ deletion | 4.6 (182) |
|                         | Other category A | 1.3 (53) |
| B: Predicted oncogenic METex14 alterations affecting METex14 skipping, exon 14 deletion, or CBL binding disruption but not included in current capmatinib CDx label | Y1003 base sub | 0.83 (33) |
|                         | Splice acceptor base sub | 0.68 (27) |
|                         | Splice PPT deletiona | 0.20 (8) |
|                         | Splice PPT base subb | 0.18 (7) |
|                         | Whole exon deletion | 0.18 (7) |
|                         | Other category B | 0.23 (9) |
| C: MET mutations with known or suspected oncogenic potential not included in category A or B | H1094Y | 0.73 (29) |
|                         | T263M | 0.55 (22) |
|                         | L1195V | 0.40 (16) |
|                         | D1228N | 0.30 (12) |
|                         | D1228H | 0.18 (7) |
|                         | Other category C | 2.7 (108) |
| D: MET mutations of unknown functional significance | R1166Q | 0.20 (8) |
|                         | L1195F | 0.20 (8) |
|                         | N1081S | 0.20 (8) |
|                         | E355K | 0.18 (7) |
|                         | V127M | 0.18 (7) |
|                         | Other category D | 54 (2,168) |

Abbreviation: PPT, polypyrimidine tract.

*aSmall subset of complex deletions that result in introduction of purines in the PPT.
*Base substitutions in the PPT at 2888-10.
| Case | METex14 Alteration (VAF) | Concurrent Driver (VAF) | Sample Type |
|------|-------------------------|-------------------------|-------------|
| 1    | 3028+3A>G (1.3)         | EGFR E746_A750del (10)  | Tissue      |
| 2    | 2888-2_2888delAGA (5.5) | EGFR E746_A750del (23)  | Tissue      |
| 3    | 3028+3A>G (1.0)         | EGFR E746_A750del (26)  | Tissue      |
| 4    | 3007T>A (3.0)           | EGFR E746_A750del (43)  | Tissue      |
| 5    | 2888-43_2888-18del26 (14)| EGFR G719A (13)        | Tissue      |
| 6    | 2888-10C>G (0.2)        | EGFR L858R (12)         | Liquid      |
| 7    | 2951_3028+23del101 (9.9)| EGFR L858R (36)         | Tissue      |
| 8    | 2888-30_2888-2del29 (21)| EGFR L858R (4.0)        | Tissue      |
| 9    | 3026_3028+38del41 (4.5) | EGFR L861Q (17)         | Tissue      |
| 10   | 2888-19_2895del27 (3.5) | ERBB2 A20T (0.22)       | Liquid      |
| 11   | 3028+2T>A (66)          | ERBB2 D1058A (34)       | Tissue      |
| 12   | 3028G>C (19)            | ERBB2 R157W (54)        | Tissue      |
| 13   | 3022_3028+6delCCAGAAGGTATAT (29)| ERBB2 S310F (17), KRAS G12S (2.1), KRAS G13D (1.9) | Tissue |
| 14   | 2888-17_2888-4del>ATAAG (45)| ERBB2 S310F (8.2)       | Tissue      |
| 15   | 2888-30_2888-5del26 (6.0)| KRAS A146P (2.0)        | Tissue      |
| 16   | 2888-20_2888-13delTTCTTCTTCT (0.84) | KRAS G12A (0.49)      | Liquid      |
| 17   | 3028G>C (12)            | KRAS G12A (42)          | Tissue      |
| 18   | 3028+3A>G (7.0)         | KRAS G12A (48)          | Tissue      |
| 19   | 3028G>A (51)            | KRAS G12A (94)          | Tissue      |
| 20   | 3028G>A (7.7)           | KRAS G12C (11)          | Tissue      |
| 21   | 3028G>C (17)            | KRAS G12C (12)          | Tissue      |
| 22   | 3028G>A (24)            | KRAS G12C (18)          | Tissue      |
| 23   | 2888-10C>G (1.0)        | KRAS G12C (19)          | Tissue      |
| 24   | 2888-1G>A (39)          | KRAS G12C (28)          | Tissue      |
| 25   | 3028+1_3028+4>AC (3.0)  | KRAS G12C (5.5)         | Tissue      |
| 26   | 3028+2T>G (2.2)         | KRAS G12D (0.18)        | Liquid      |
| 27   | 3017_3028+1delTTCTTCTCCAGAAGG (21)| KRAS G12D (1.8) | Tissue     |
| 28   | 3028G>A (16)            | KRAS G12D (17)          | Tissue      |
| 29   | 3028+1G>A (11)          | KRAS G12D (22)          | Tissue      |
| 30   | 2888-17_2898del128 (60) | KRAS G12D (4.8)         | Tissue      |
| 31   | 2888-19_2895del27 (2.2) | KRAS G12D (7.8)         | Liquid      |
| 32   | 3028+3A>G (29)          | KRAS G12D (86)          | Tissue      |
| 33   | 3028G>A (0.31)          | KRAS G12R (0.32)        | Liquid      |
| 34   | 3028+1G>A (30)          | KRAS G12R (2.0)         | Tissue      |
| 35   | 2888-15_2888-2delTCTCTCTTCTTTAA (19)| KRAS G12S (18) | Tissue     |
| 36   | 3028+1G>A (30)          | KRAS G12S (3.0)         | Tissue      |
| 37   | 3028+1G>T (9.8)         | KRAS G12S (31)          | Tissue      |
| 38   | 3028G>T (19)            | KRAS G12V (12)          | Tissue      |
| 39   | 3028+1G>T (4.0)         | KRAS G12V (2.8)         | Tissue      |
| 40   | 2888-1G>A (22)          | KRAS G12V (21)          | Tissue      |
| 41   | 2888-16_2891del120 (22)| KRAS G12V (37)          | Tissue      |
| 42   | 3028+2T>C (19)          | KRAS G12V (42)          | Tissue      |
| 43   | 2888-30_2888-15delAACAGCTTTCTTTCTTT (73)| KRAS G12V (5.4) | Tissue     |
| 44   | 3028+2T>C (7.2)         | KRAS G13C (1.2)         | Tissue      |

(Continued on following page)
### Table A3. NSCLC Samples With METex14 Alterations and Co-occurring Known Driver Alterations (Continued)

| Case | METex14 Alteration (VAF) | Concurrent Driver (VAF) | Sample Type |
|------|--------------------------|-------------------------|-------------|
| 45   | 3028G>T (15)             | KRAS G13C (18)          | Tissue      |
| 46   | 3028delG (42)            | KRAS G13C (52)          | Tissue      |
| 47   | 2888-10_2891del14 (26)   | KRAS G13C (74), KRAS G12V (74) | Tissue |
| 48   | 2888-62_2888-14del49 (18) | KRAS G13D (25)          | Tissue      |
| 49   | 3008A>C (32)             | KRAS G13D (33)          | Tissue      |
| 50   | 2888-17_2888-2del16 (54) | KRAS G13D (36)          | Tissue      |
| 51   | 3028G>A (21)             | KRAS G13D (8.7)         | Tissue      |
| 52   | 3028+1_3028+13del13 (19) | KRAS K117N (23)         | Tissue      |
| 53   | 3028G>A (0.79)           | KRAS K117R (1.4)        | Liquid      |
| 54   | 2888-36_2888-30delGTCTTTA (58) | KRAS L19F (1.0)    | Tissue      |
| 55   | 2888-30_2907del150 (4.0) | KRAS L19F (12), KRAS Q61E (3.4) | Tissue |
| 56   | 3028G>A (3.0)            | KRAS Q61L (4.0)         | Tissue      |
| 57   | 3028+1G>T (1.3)          | KRAS Q61R (0.52)        | Liquid      |
| 58   | 3028G>C (31)             | KRAS V14I (0.64)        | Liquid      |
| 59   | 3028+2T>C (15)           | KRAS V14I (1.4)         | Tissue      |
| 60   | 3028+1G>A (22)           | RET-NA RE               | Tissue      |
| 61   | 3028+3A>T (1.7)          | RET-PHF20L1 RE          | Liquid      |
| 62   | 3028G>C (1.9)            | ROS1-CD74 RE            | Tissue      |

Abbreviations: NSCLC, non–small-cell lung cancer; RE, rearrangement; VAF, variant allele frequency.
| Specimen | cTF of Liquid Specimen (%) | Days Between Specimen Collection | METex14 Alteration                  | Concordance Status |
|----------|----------------------------|----------------------------------|------------------------------------|--------------------|
| 1        | 0.50                       | 1                                | 3026_3028+1delAAGG                 | Concordant         |
| 2        | 15                         | 10                               | 3019_3028del10                     | Concordant         |
| 3        | 1.3                        | 13                               | 2888-15_2888-14insAGT              | Concordant         |
| 4        | 1.3                        | 6                                | 3022_3028-4del11                   | Concordant         |
| 5        | 2.4                        | 10                               | D1010N                             | Concordant         |
| 6        | 0.21                       | 17                               | 2888-21_2888-13>AAGCT              | Concordant         |
| 7        | 0.21                       | 17                               | 2888-17_2888-3del15                | Concordant         |
| 8        | 0.62                       | 372                              | D1010N                             | ctDNA-negative     |
| 9        | 2.1                        | 17                               | 3028+1G>C                          | Concordant         |
| 10       | 0.90                       | 17                               | 3028+1G>C                          | Concordant         |
| 11       | 2.6                        | 590                              | D1010fs*5                          | Concordant         |
| 12       | 1.1                        | 705                              | 2920_3028+10del119                 | Concordant         |
| 13       | 0.96                       | 963                              | 2888-10C>G                         | Tissue-negative bunk |
| 14       | 0.32                       | 979                              | 3028+3A>G                          | Concordant         |

NOTE. In 10 of 14 pairs, the tissue specimen was collected first, and in four of 14 pairs, the liquid specimen was collected first. Abbreviations: ctDNA, circulating tumor DNA; cTF, comprehensive tumor fraction.

*Both tissue and liquid samples from this patient harbored an EGFR L858R mutation, and the METex14 alteration was only present in the second sample along with BRAF D594N and EGFR T790M acquired postafatinib treatment.
### TABLE A5. NSCLC Cases With Multiple METex14 Alterations Detected

| Case | METex14 Alterations (VAF) | Cis or Trans | Sample Type |
|------|--------------------------|--------------|-------------|
| 1    | D1010Y (2.8) 2888-1G>C (2.5) | Unknown | ctDNA |
| 2    | 3028+2T>G (38) 2888-5_2890>ATA (33) | Cis | Tissue |
| 3    | 2888-1G>T (37) 3003-3028+6del32 (31) | Unknown | Tissue |
| 4    | 2888-1G>T (50) 3028+2T>C (9.0) | Cis | Tissue |
| 5    | 3028+1G>A (21) D1010N (11) | Trans | Tissue |
| 6    | 3028+3A>T (52) 2888-1G>C (29) | Unknown | Tissue |
| 7    | 2888-19_2888-13>AAA (62) 3028+3A>T (11) | Unknown | Tissue |
| 8    | 3028+2T>C (43) | NA | Tissue (RUL) |
| 8    | Y1003F (31) 3028+2T>C (3.0) | Trans | Tissue (RML) |
| 9    | 3028+1G>T (6.0) R1004_D1010del (2.0) | Trans | Tissue |
| 9    | R1004_D1010del (76) | NA | Tissue |

Abbreviations: ctDNA, circulating tumor DNA; NA, not applicable; NSCLC, non-small-cell lung cancer; RML, right middle lung; RUL, right upper lung; VAF, variant allele frequency.

aThe second tissue specimen for case 8 showing multiple METex14 alterations was collected 286 days after the first tissue specimen.
bThe second tissue specimen for case 9 was collected 886 days after the first tissue specimen.
### TABLE A6. \(\textit{MET}\textsubscript{ex14}\) Alterations in Patients Who Received \(\textit{MET}\textsubscript{i}\)

| Case | \(\textit{MET}\textsubscript{ex14}\) Alteration | \(\textit{MET}\textsubscript{i}\) Line\(^a\) | \(\textit{MET}\textsubscript{i}\) | rwR | TTD (months) | Censored | ECOG\(^a\) |
|------|---------------------------------|--------------------------------|--------------------------------|------|-------------|----------|----------|
| 1    | 2888-70_2976>18                 | 1                              | Crizotinib                     | PR   | 43          | Yes      | NA       |
| 2    | 2888-28_2888-9del20             | 1                              | Crizotinib                     | SD   | 22          | Yes      | 1        |
| 3    | 3028+1G>A                       | 2                              | Crizotinib                     | SD   | 21          | No       | 0        |
| 4    | 3028+1G>T                       | 2                              | Crizotinib                     | SD   | 13          | No       | NA       |
| 5    | 3028+1G>T                       | 4                              | Crizotinib + IO                | SD   | 13          | No       | 0        |
| 6    | 3028G>A                         | 7                              | Crizotinib                     | PR   | 10          | No       | NA       |
| 7    | 3028delG                        | 1                              | Crizotinib                     | CR   | 9.5         | Yes      | 0        |
| 8    | 3028G>A                         | 2                              | Crizotinib                     | SD   | 9.1         | No       | NA       |
| 9    | 2888-23_2895del31               | 1                              | Crizotinib                     | PR   | 8.1         | No       | NA       |
| 10   | 2888-14_2888-4delCTCTCTGT TT    | 2                              | Crizotinib                     | PR   | 6.8         | No       | 1        |
| 11   | 2888-16_2888-4delTTCTCTCTGT TT  | 3                              | Crizotinib                     | SD   | 6.4         | No       | NA       |
| 12   | 3028+3A>T                       | 3                              | Crizotinib                     | PR   | 6.3         | No       | 1        |
| 13   | 3028+1G>A                       | 3                              | Crizotinib                     | SD   | 5.0         | No       | 1        |
| 14   | 3028+3A>T                       | 2                              | Crizotinib                     | SD   | 5.5         | Yes      | 1        |
| 15   | 2888-16_2888-4delTTCTCTCTGT TT  | 3                              | Crizotinib + chemo             | PR   | 5.4         | No       | NA       |
| 16   | 2888-35_2888-1del36             | 1                              | Crizotinib                     | PR   | 5.3         | No       | NA       |
| 17   | 2888-27_2888-10del18            | 5                              | Crizotinib                     | CR   | 4.9         | No       | 2        |
| 18   | 3028+1G>A                       | 3                              | Crizotinib                     | NA   | 4.8         | No       | NA       |
| 19   | 3028+3A>T                       | 1                              | Crizotinib                     | PR   | 4.6         | No       | NA       |
| 20   | 3028G>A                         | 2                              | Crizotinib                     | SD   | 4.5         | No       | 2        |
| 21   | 2888-29_2920del62               | 3                              | Crizotinib                     | PR   | 4.4         | No       | NA       |
| 22   | 3009_3028+13del33               | 4                              | Cabozantinib                   | NA   | 4.3         | No       | 0        |
| 23   | 2888-48_2888-30del19            | 1                              | Crizotinib                     | NA   | 3.7         | Yes      | 2        |
| 24   | 3000_3028+9del38                | 1                              | Crizotinib                     | PR   | 3.7         | No       | NA       |
| 25   | 3028+1G>A                       | 1                              | Crizotinib                     | PD   | 3.0         | No       | 2        |
| 26   | 3005_3028+11del35               | 4                              | Crizotinib                     | SD   | 2.8         | No       | 2        |
| 27   | 3028G>A, 3028+1G>A              | 3                              | Crizotinib                     | SD   | 2.7         | No       | NA       |
| 28   | 2907_3028+49del171              | 2                              | Crizotinib                     | PD   | 2.7         | No       | 0        |
| 29   | 3028+2_3028+3TA>GT              | 2                              | Crizotinib                     | NA   | 2.6         | No       | 1        |
| 30   | 2888-18_2888-9delCTTCTCTCT      | 4                              | Crizotinib                     | PD   | 2.3         | No       | NA       |
| 31   | 3028+2_3028+10delTATATATCA      | 2                              | Crizotinib + IO               | PR   | 2.2         | No       | 3        |
| 32   | 3028G>A                         | 1                              | Crizotinib                     | PR   | 2.0         | Yes      | NA       |
| 33   | 2888-21_2913del47               | 2                              | Crizotinib                     | NA   | 1.9         | Yes      | 2        |
| 34   | 2888-18_2892del23               | 2                              | Crizotinib                     | SD   | 1.6         | No       | 2        |
| 35   | 3028G>C                         | 1                              | Crizotinib                     | SD   | 1.5         | No       | 3        |
| 36   | 2888-32_2889del34               | 3                              | Crizotinib                     | NA   | 1.5         | Yes      | 0        |
| 37   | 3028G>C                         | 2                              | Crizotinib                     | NA   | 0.62        | No       | NA       |
| 38   | 3009_3028+10del30               | 3                              | Crizotinib                     | NA   | 0.62        | No       | 2        |
| 39   | 3028+2T>C                       | 1                              | Crizotinib                     | NA   | 0.46        | Yes      | 1        |
| 40   | 2888-40_2888-23del18            | 1                              | Crizotinib                     | PD   | 0.33        | No       | 1        |
| 41   | 3028+1G>A                       | 3                              | Crizotinib                     | NA   | 0.26        | Yes      | 1        |
| 42   | 3007T>A                         | 1                              | Crizotinib                     | NA   | 0.07        | No       | NA       |

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; IO, immunotherapy; NA, not available; PD, progressive disease; PR, partial response; rwR, real-world response; SD, stable disease; TKI, tyrosine kinase inhibitor; TTD, time to treatment discontinuation.

\(^a\)Reported for 25 patients with an ECOG performance score recorded up to 30 days before or within 7 days after \(\textit{MET}\textsubscript{TKI}\) start.