RESEARCH ARTICLE

Atezolizumab Treatment of Tumors with High Tumor Mutational Burden from MyPathway, a Multicenter, Open-Label, Phase IIa Multiple Basket Study

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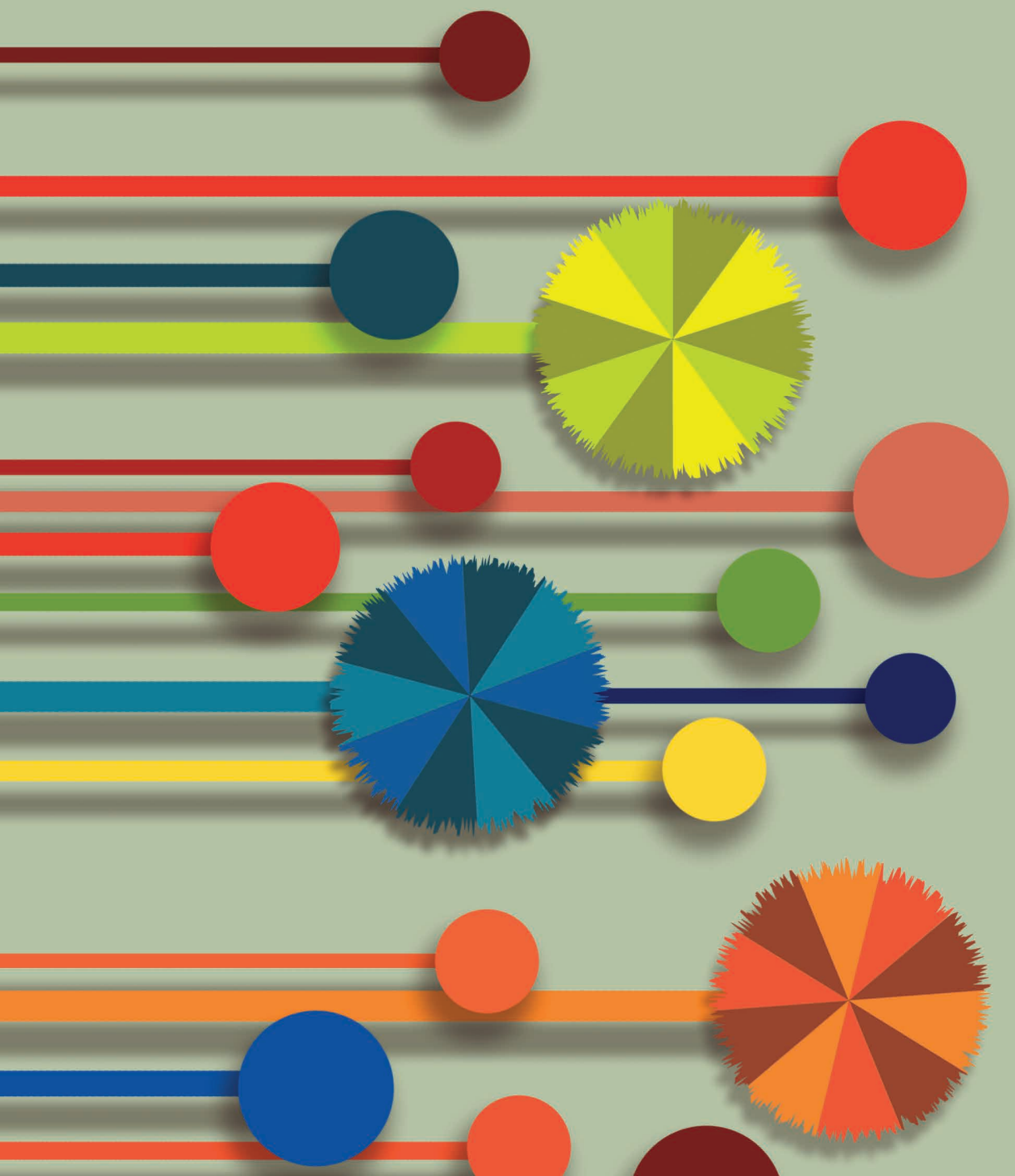

ABSTRACT High tumor mutational burden (TMB-H) correlates with improved immunotherapy response. We assessed atezolizumab 1,200 mg every 3 weeks for TMB-H tumors from MyPathway (NCT02091141), a phase IIa multibasket study. One hundred twenty-one patients had advanced solid tumors with TMB ≥10 mut/Mb by any Clinical Laboratory Improvement Amendments (CLIA)–certified assay. The preplanned primary endpoint was objective response rate (ORR) in patients with TMB ≥16 mut/Mb tumors by FoundationOne TMB testing [F1(CDx)]. Patients with F1(CDx) TMB ≥10 and <16 mut/Mb were also evaluated. Ninety patients with 19 tumor types and F1(CDx) TMB ≥10 mut/Mb were efficacy evaluable. In 42 patients with F1(CDx) TMB ≥16 mut/Mb, confirmed ORR was 38.1% [16/42; 95% confidence interval (CI), 23.6–54.4], and disease control rate was 61.9% (26/42; 95% CI, 45.6–76.4) versus 2.1% (1/48; 95% CI, 0.1–11.1) and 22.9% (11/48; 95% CI, 12.0–37.3) for 48 patients with TMB ≥10 and <16 mut/Mb. Responses were observed in nine different tumor types (47%; 9/19).

SIGNIFICANCE: Atezolizumab monotherapy had promising, durable clinical activity across a variety of advanced solid tumor types in patients with TMB ≥16 mut/Mb tumors lacking other suitable treatment options and who were immunotherapy-naïve at enrollment, regardless of microsatellite instability status. Limited activity was observed in tumors with TMB ≥10 and <16 mut/Mb.

See related commentary by Maron and Klempner, p. 602.

INTRODUCTION

High tumor mutational burden (TMB-H) is accompanied by elevated neoantigen expression in a variety of tumor types, potentially rendering those tumors more responsive to cancer immunotherapy (1, 2). Recent studies have associated TMB-H status with improved response to immune checkpoint inhibitors, including those targeting the PD-1/PD-L1 pathway (1–3). Approximately 16.4% of cancers are characterized as TMB-H, defined as TMB ≥10 mut/Mb, and 7.3% have TMB ≥20 mut/Mb, with significant variability in TMB levels between cancer types (4–6).

In June 2020, pembrolizumab, a humanized antibody targeting PD-1, became the first drug approved by the FDA for tumors characterized as TMB-H based on data from the KEYNOTE-158 phase II basket study (7, 8). The FoundationOne CDx assay for TMB was approved by the FDA as a companion diagnostic. Among 102 patients with FoundationOne CDx-assessed TMB ≥10 mut/Mb tumors, the objective response rate (ORR) was 29% [30/102; 95% confidence interval (CI), 21–39; ref. 8]. In patients with TMB <10 mut/Mb tumors, ORR was 6% (43/688; 95% CI, 5–8). However, interpretation of these data is somewhat limited as enrollment in KEYNOTE-158 was restricted to 10 solid-tumor types, most commonly small-cell lung (34/102), cervical (16/102), and endometrial (15/102) cancers in the TMB ≥10 mut/Mb group, and excluded highly prevalent cancers such as colon and breast cancers. Recent reports suggest that immunotherapy activity in TMB-H tumors may be influenced by the clinical and molecular features of different tumor types, and as such it remains unclear whether a single TMB cutoff can be appropriately applied to a pan-tumor population (9–11).

Atezolizumab is an anti–PD-L1 mAb that enhances tumor-specific T-cell responses, resulting in improved antitumor activity and clinical outcomes (12, 13). Atezolizumab is currently approved by the FDA as a monotherapy for urothelial carcinoma and non–small cell lung cancer (NSCLC) or as part of a combination regimen for NSCLC, small-cell lung cancer, hepatocellular carcinoma, and melanoma (14). Recent reports have indicated that elevated TMB in the tumor tissue of patients with NSCLC, metastatic urothelial carcinoma, and melanoma is associated with improved atezolizumab efficacy (15–17). Furthermore, retrospective analyses suggest that a TMB cutoff of ≥16 mut/Mb may enrich for response to atezolizumab in various tumor types (17) and may best balance undertreatment versus overtreatment of patients. However, prospective data remain limited regarding the activity of atezolizumab in tumors with TMB ≥16 mut/Mb.

MyPathway (NCT02091141), an open-label, multicenter, nonrandomized, multiple basket phase IIa study, evaluates the activity of established targeted therapies outside of their FDA-approved indications in patients with advanced solid tumors carrying potentially actionable genetic or molecular alterations and no other suitable therapy options (ref. 18; Supplementary Fig. S1). Here, we present results for the efficacy and safety of atezolizumab treatment in patients with tumors characterized by TMB ≥10 mut/Mb, agnostic of tumor site of origin. The preplanned primary efficacy

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Note: Supplementary data for this article are available at Cancer Discovery Online (http://cancerdiscovery.aacrjournals.org/).

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Cancer Discov 2022;12:654–69

doi: 10.1158/2159-8290.CD-21-0450

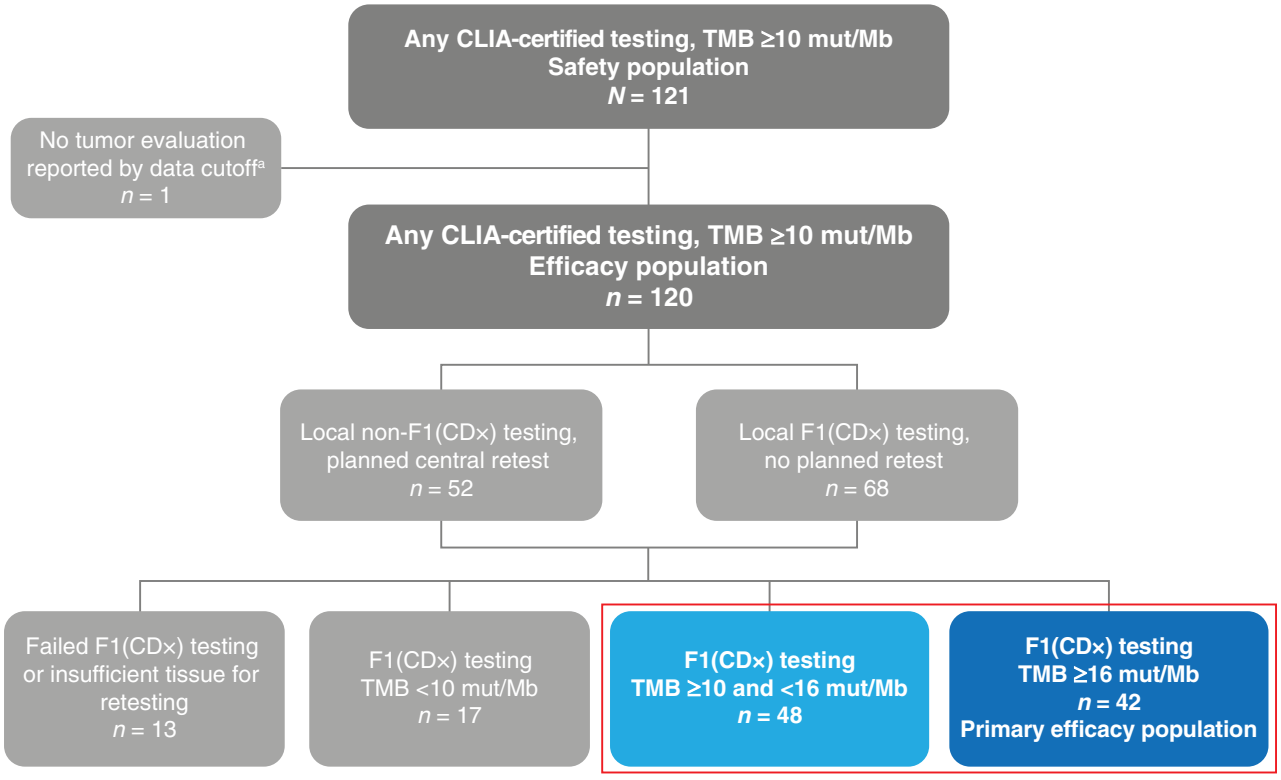

Figure 1. TMB local and central testing. One hundred and twenty-one patients treated with atezolizumab in MyPathway were included in the safety population. Among these patients, one with TMB ≥10 and <16 mut/Mb did not have a tumor evaluation by the data cutoff and was not included in the efficacy analysis. Based on local or central F1(CDx) TMB testing, 42 patients had tumors with TMB ≥16 mut/Mb and comprised the primary efficacy population, and 48 patients had tumors with TMB ≥10 and <16 mut/Mb. Thirty patients had TMB <10 mut/Mb upon retrospective F1(CDx) testing or did not have an F1(CDx) testing result, and were not included in the F1(CDx) efficacy-evaluable population. [a]Patient had TMB ≥10 and <16 mut/Mb by any CLIA-certified and F1(CDx) testing. CDx, Companion Diagnostic; CLIA, Clinical Laboratory Improvement Amendments; F1, FoundationOne.

endpoint was ORR in patients with TMB ≥16 mut/Mb tumors by FoundationOne or FoundationOne CDx [F1(CDx)] testing; responses were also assessed in patients with F1(CDx) TMB ≥10 and <16 mut/Mb tumors. Secondary endpoints included disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. Exploratory analyses were performed in patients with TMB ≥16 mut/Mb and TMB ≥10 and <16 mut/Mb tumors assessed by any TMB assay conducted in a certified Clinical Laboratory Improvement Amendments (CLIA) laboratory (i.e., any CLIA-certified assay) and by tumor type and biomarker subgroups.

RESULTS

Patients

Patients in this analysis were enrolled between August 28, 2018, and July 9, 2020, from 32 study sites. All patients had TMB ≥10 mut/Mb advanced solid tumors, as locally assessed by any CLIA-certified assay for the purposes of enrollment. As of the January 19, 2021, data cutoff date, 121 patients had received at least one dose of study drug, of whom 120 were efficacy- evaluable (Fig. 1). To limit variability in TMB measurements observed between different assays (19, 20), patients without F1(CDx) TMB testing at enrollment provided tissue for retrospective central F1(CDx) retesting for the primary efficacy analysis. In patients with local or central F1(CDx) TMB testing results, 42 had TMB ≥16 mut/Mb tumors, comprising the primary efficacy population, and 49 had TMB ≥10 and <16 mut/Mb tumors, of whom 48 were efficacy evaluable (Fig. 1). Seventeen patients had tumors that fell beneath the 10 mut/Mb threshold required for inclusion in the F1(CDx) efficacy analysis upon central retesting, whereas 13 patients had insufficient tissue or failed F1(CDx) retesting.

At the data cutoff, 10.7% (13/121) of all patients remained on treatment, including 23.8% (10/42) of patients with F1(CDx) TMB ≥16 mut/Mb and 2.0% (1/49) of those with F1(CDx) TMB ≥10 and <16 mut/Mb tumors. Additionally, 60.3% (73/121) of all patients had discontinued the study, and 28.9% (35/121) had discontinued treatment but remained in follow-up (Supplementary Fig. S2). The most common reason for treatment discontinuation was progression of disease [PD; 83.3% (90/108)]. Median follow-up from treatment initiation was 9.9 (range, 0.2–25.6) months. Baseline patient and disease characteristics were generally balanced between the F1(CDx) TMB cohorts, although the TMB ≥10 and <16 mut/Mb cohort had higher proportions of female patients, patients with ≥3 prior lines of therapy, and patients with low PD-L1 IHC staining scores, as well as fewer patients with high microsatellite instability (MSI-H) tumors compared with the TMB ≥16 mut/Mb cohort (Table 1).

Table 1. Baseline demographics and clinical characteristics (*N* = 121)

	F1(CDx) assay		Any CLIA-certified assay		
Characteristic	≥16 mut/Mb *n* = 42	≥10 and <16 mut/Mb *n* = 49	≥16 mut/Mb *n* = 56	≥10 and <16 mut/Mb *n* = 65	Total *N* = 121
Median age, years (range)	67 (25–90)	66 (44–85)	67 (25–90)	66 (32–85)	67 (25–90)
Sex, *n* (%)					
Female	19 (45.2)	35 (71.4)	29 (51.8)	45 (69.2)	74 (61.2)
Male	23 (54.8)	14 (28.6)	27 (48.2)	20 (30.8)	47 (38.8)
Race, *n* (%)					
White	37 (88.1)	34 (69.4)	48 (85.7)	43 (66.2)	91 (75.2)
Black/African American	3 (7.1)	7 (14.3)	5 (8.9)	8 (12.3)	13 (10.7)
Asian	0	4 (8.2)	0	8 (12.3)	8 (6.6)
American Indian/Alaska native	1 (2.4)	1 (2.0)	1 (1.8)	2 (3.1)	3 (2.5)
Other	1 (2.4)	3 (6.1)	2 (3.6)	4 (6.2)	6 (5.0)
Ethnicity, *n* (%)					
Not Hispanic or Latino	36 (85.7)	43 (87.8)	49 (87.5)	57 (87.7)	106 (87.6)
Hispanic or Latino	4 (9.5)	4 (8.2)	4 (7.1)	5 (7.7)	9 (7.4)
Undesignated[a]	2 (4.8)	2 (4.1)	3 (5.4)	3 (4.6)	6 (5.0)
ECOG PS, *n* (%)	*n* = 42	*n* = 49	*n* = 55	*n* = 65	*n* = 120
0	11 (26.2)	17 (34.7)	18 (32.7)	20 (30.8)	38 (31.7)
1	31 (73.8)	32 (65.3)	37 (67.3)	45 (69.2)	82 (68.3)
Median prior lines of therapy for metastatic disease (range)	*n* = 36 2 (1–11)	*n* = 48 3 (1–10)	*n* = 50 3 (1–11)	*n* = 64 3 (1–11)	*n* = 114 3 (1–11)
Prior lines of therapy for metastatic disease, *n* (%)					
1	9 (21.4)	9 (18.4)	9 (16.1)	14 (21.5)	23 (19.0)
2	13 (31.0)	8 (16.3)	15 (26.8)	11 (16.9)	26 (21.5)
3	5 (11.9)	8 (16.3)	8 (14.3)	14 (21.5)	22 (18.2)
4	4 (9.5)	6 (12.2)	5 (8.9)	7 (10.8)	12 (9.9)
5+	5 (11.9)	17 (34.7)	13 (23.2)	18 (27.7)	31 (25.6)
Missing	6 (14.3)	1 (2.0)	6 (10.7)	1 (1.5)	7 (5.8)
MSI status, *n* (%)	*n* = 40	*n* = 47	*n* = 53	*n* = 63	*n* = 116
High	11 (27.5)	1 (2.1)	13 (24.5)	1 (1.6)	14 (12.1)
Stable or low	29 (72.5)	46 (97.9)	38 (71.7)	62 (98.4)	100 (86.2)
Indeterminate	0	0	2 (3.8)	0	2 (1.7)
PD-L1[b] TPS score, *n* (%)	*n* = 26	*n* = 29	*n* = 34	*n* = 37	*n* = 71
<1	15 (57.7)	24 (82.8)	20 (58.8)	33 (89.2)	53 (74.6)
≥1 and <50	5 (19.2)	5 (17.2)	8 (23.5)	4 (10.8)	12 (16.9)
≥50	6 (23.1)	0	6 (17.6)	0	6 (8.5)
PD-L1[b] CPS score[c], *n* (%)	*n* = 23	*n* = 22	*n* = 29	*n* = 29	*n* = 58
<1	4 (17.4)	14 (63.6)	7 (24.1)	19 (65.5)	26 (44.8)
≥1 and <50	14 (60.9)	8 (36.4)	17 (58.6)	10 (34.5)	27 (46.6)
≥50	5 (21.7)	0	5 (17.2)	0	5 (8.6)

Abbreviations: CDx, Companion Diagnostic; CPS, combined positive scores; ECOG PS, Eastern Cooperative Oncology Group performance status; F1, FoundationOne; TPS, tumor proportion scores.

[a]"Undesignated" includes patients with ethnicity not reported or unknown.

[b]PD-L1 IHC testing was conducted using the clone 22C3 pharmDx kit. Patients not reported here had no local PD-L1 test result and no tissue or insufficient tissue for central testing. Two patients overall also had PD-L1 amplification.

[c]CPS scores were not always reported as part of the local PD-L1 assay results in pathology reports.

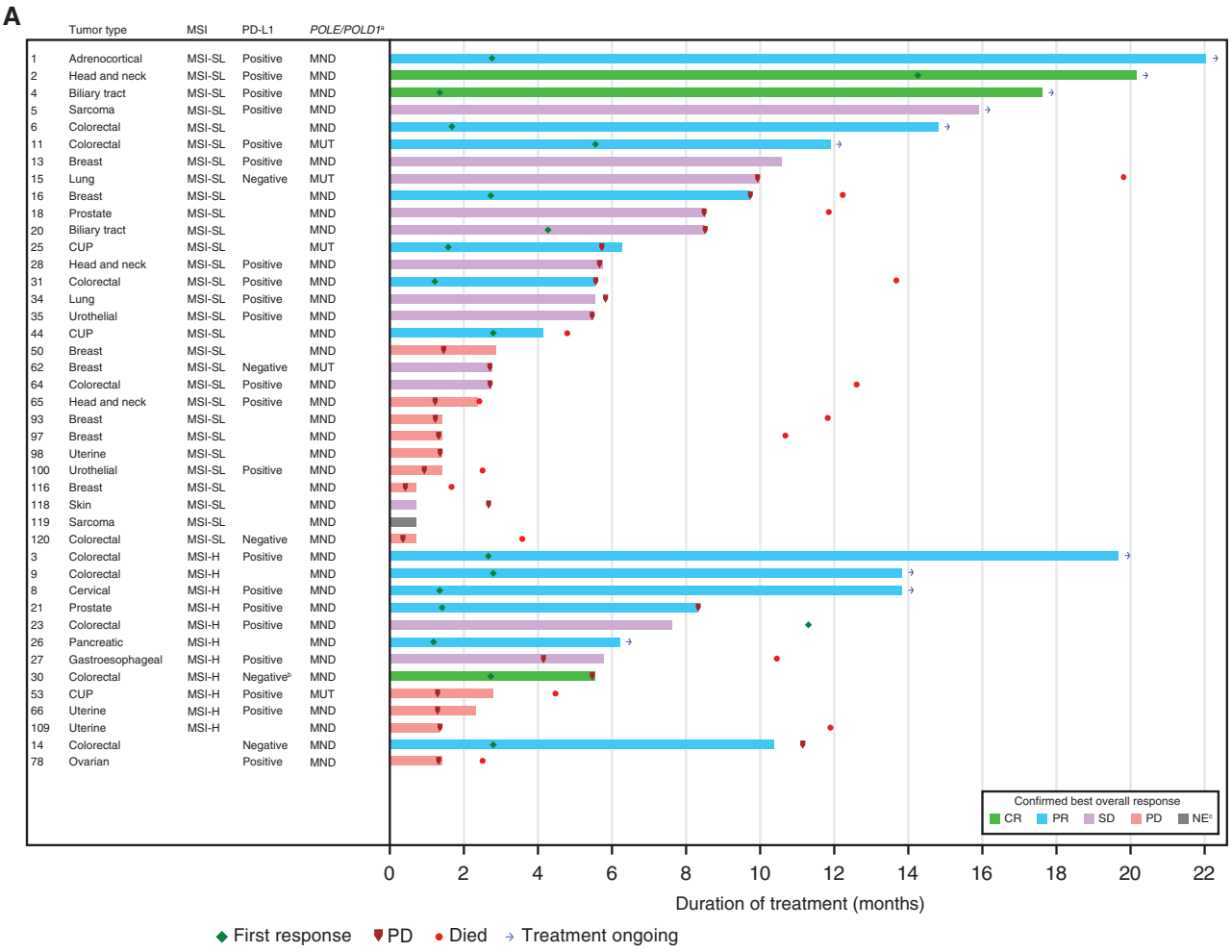

Figure 2. Time on treatment in patients with F1(CDx) TMB testing. **A,** Patients with TMB ≥16 mut/Mb tumors ($n = 42$). (*continued on following page*)

Clinical Outcomes in Patients by F1(CDx) TMB Cohort

In the per-protocol primary analysis population of 42 patients with F1(CDx) TMB ≥16 mut/Mb tumors, median treatment duration was 5.0 months (median of 8.0 cycles; range, 1–31; Fig. 2A). Sixteen patients had a confirmed investigator-assessed objective response by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, including three complete responses (CR) and 13 partial responses (PR); median DOR had not been reached as of the data cutoff. Confirmed ORR was 38.1% (16/42; 95% CI, 23.6–54.4) and DCR [best response of CR, PR, or stable disease (SD) >4 months] was 61.9% (26/42; 95% CI, 45.6–76.4).

One patient with a TMB ≥10 and <16 mut/Mb tumor did not have an efficacy evaluation reported by the data cutoff date and was not included in the efficacy population. In the 48 efficacy-evaluable patients with F1(CDx) TMB ≥10 and <16 mut/Mb tumors, clinical outcomes were inferior to those observed for the TMB ≥16 mut/Mb cohort. Median treatment duration was 1.4 months (median of 3.0 cycles; range, 1–18; Fig. 2B). One patient achieved a confirmed PR, for an ORR of 2.1% (1/48; 95% CI, 0.1–11.1); DCR was 22.9% (11/48; 95% CI, 12.0–37.3). The difference in ORR between patients with TMB ≥16 mut/Mb versus TMB ≥10 and <16 mut/Mb tumors was statistically significant, with an estimated difference of 36% (95% CI, 19.6–65.7).

Median PFS was 5.7 months (95% CI, 2.7–8.5) versus 1.8 months (95% CI, 1.4–2.6) in patients with TMB ≥16 mut/Mb and TMB ≥10 and <16 mut/Mb tumors, respectively (Fig. 3A), and median OS was 19.8 months [95% CI, 11.9–not evaluable (NE)] versus 11.4 months (95% CI, 5.3–15.7; Fig. 3B). PFS [hazard ratio (HR), 0.34; 95% CI, 0.21–0.57; $P < 0.0001$] and OS (HR, 0.53; 95% CI, 0.29–0.97; $P = 0.0371$) were significantly longer in patients with TMB ≥16 mut/Mb versus TMB ≥10 and <16 mut/Mb tumors.

Of the 13 patients lacking central F1(CDx) retesting data and omitted from the primary analysis for ORR, six had TMB ≥16 mut/Mb tumors by any CLIA-certified assay. None of the six patients had a confirmed objective response. In a sensitivity analysis for finite sample bias, inclusion of these six patients in the F1(CDx) TMB ≥16 mut/Mb cohort produced an ORR estimate of 33.3% (16/48; 95% CI, 20.4–48.4).

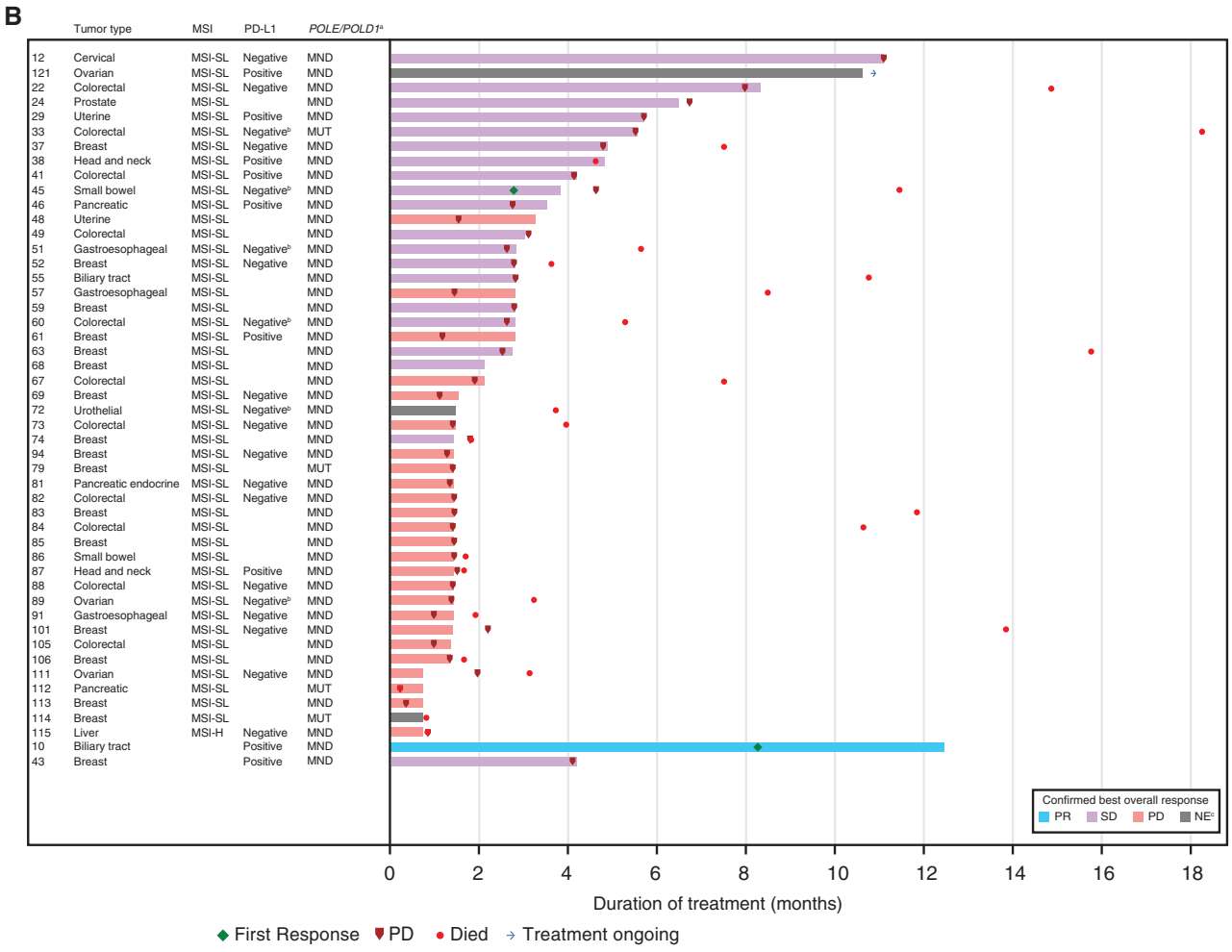

Figure 2. ***(Continued)*** **B,** Patients with TMB ≥10 and <16 mut/Mb tumors ($n = 49$). Patients with ongoing treatment at data cutoff and timepoints for first response, disease progression, and death are shown. Termination points of the treatment bars represent three weeks after the date of the last drug administration. [a]*POLE/POLD1* mutations refer to mutations in the exonuclease domains only. [b]Patient had a tumor proportion score <1 and no combined positive score. [c]Patients 72, 114, and 119 discontinued treatment without a tumor assessment and were considered to be nonresponders. Patient 121 did not have an efficacy evaluation reported by the data cutoff date and was not included in the efficacy population. CDx, Companion Diagnostic; CUP, carcinoma of unknown primary; MND, mutation not detected; MUT, mutated; NE, not evaluable; PD, progressive disease.

To assess whether imbalances in baseline characteristics between the F1(CDx) TMB ≥16 mut/Mb versus TMB ≥10 and <16 mut/Mb cohorts affected ORR, we adjusted for gender and number of prior lines of treatment in estimating ORR as if balance for these variables was achieved between the two cohorts. We found that the adjusted ORR (36.4%; 95% CI, 22.1–51.0) differed only slightly from the primary endpoint for patients with TMB ≥16 mut/Mb tumors.

In addition to the analyses of ORR based on an F1(CDx) TMB cutoff of 16 mut/Mb, we plotted estimates of ORR at TMB cutoffs from 10 to 40 mut/Mb in increments of 3 mut/Mb. A significant trend for association of ORR with TMB cutoff was observed (log OR of response for an increase of 1 mut/Mb to the cutoff: 0.061; 95% CI, 0.026–0.095; Supplementary Fig. S3; Supplementary Table S1). This trend remained significant when different cutoffs were used (TMB of 10–30 mut/Mb in intervals of 2 mut/Mb, or TMB of 10, 16, 20, and 25 mut/Mb).

Prior to the enrollment of patients in the current analysis, a separate cohort of 53 patients was enrolled in the MyPathway atezolizumab arm based on an earlier protocol version, with patients assessed for response using immune-modified RECIST. Of 41 patients with known F1(CDx) TMB at enrollment, 28 had TMB ≥16 mut/Mb tumors. An exploratory analysis showed immune-modified ORR was 21.4% (6/28) in this population (Supplementary Table S2). Consistent with observations from the primary efficacy analysis, no responders were observed among the 13 patients with F1(CDx) TMB <16 mut/Mb tumors.

Local versus Central TMB Testing

Among all 121 patients enrolled in this analysis, 56 had TMB ≥16 mut/Mb and 65 had TMB ≥10 and <16 mut/Mb tumors by local TMB testing using any CLIA-certified assay. The local TMB testing assays used for patient enrollment are detailed in Supplementary Table S3. Among the 120 efficacy-evaluable

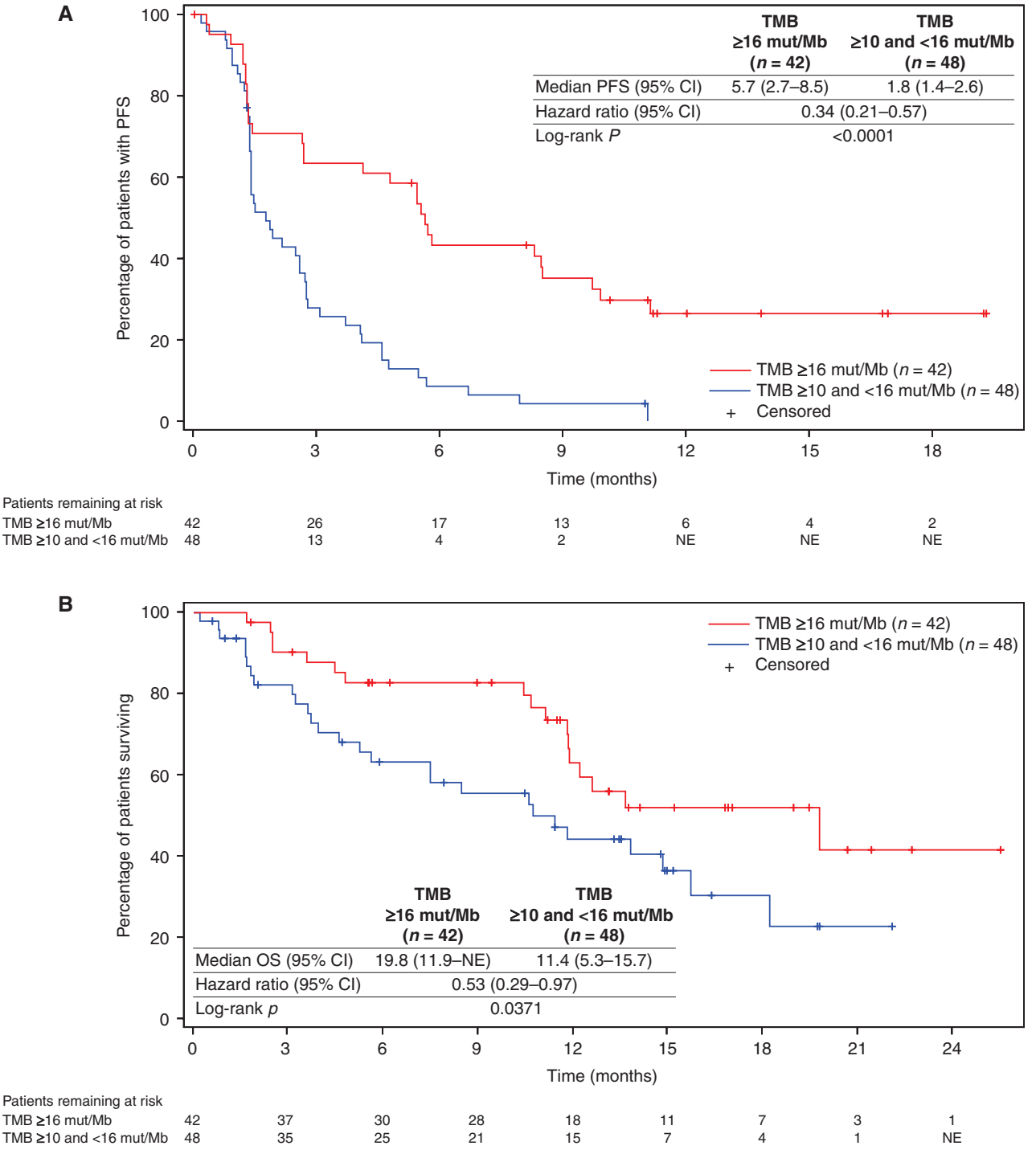

Figure 3. PFS and OS in efficacy-evaluable patients with F1(CDx) TMB testing ($n = 90$). **A,** PFS in patients with TMB ≥16 mut/Mb versus TMB ≥10 and <16 mut/Mb tumors. **B,** OS in patients with TMB ≥16 mut/Mb versus TMB ≥10 and <16 mut/Mb tumors. CDx, Companion Diagnostic; CI, confidence interval; F1, FoundationOne; TMB, tumor mutational burden.

patients, 68 had local F1(CDx) TMB testing, and 52 were enrolled based on a non-F1(CDx) CLIA-certified assay, of whom 39 subsequently had TMB results from both local non-F1(CDx) testing and central F1(CDx) retesting (Fig. 1). In these 39 patients, median time from the collection of the tissue sample used for TMB testing to enrollment was 228 days (range, 1–5,736). Overall agreement for classification into TMB <16 mut/Mb versus TMB ≥16 mut/Mb cohorts was observed for 74.4% (29/39; 95% CI, 57.9–87.0) of these patients, including nine patients with TMB ≥16 mut/Mb tumors on both assays. The remaining 13 of 52 patients had a failed F1(CDx) assay or had insufficient tissue for retesting.

The correlation between local non-F1(CDx) and central F1(CDx) TMB results is shown in Supplementary Fig. S4A and S4B for 24 patients with both assays performed from the same tissue sample (R^2 = 0.9129; P < 0.0001). In 13 patients with local and central assays performed from different tissue samples, R^2 was 0.9685 (P < 0.0001). Agreement for local versus central TMB testing results by number of patients is shown in Supplementary Table S4.

No confirmed responses were observed among the nine patients with TMB ≥16 mut/Mb by any CLIA-certified assay and TMB <16 mut/Mb by F1(CDx), or in the 17 patients with TMB <10 mut/Mb tumors by F1(CDx) retesting. Among the 13 patients without F1(CDx) testing results, one patient with a TMB ≥10 and <16 mut/Mb tumor by any CLIA-certified assay had a PR.

Clinical Outcomes in Patients with TMB by Any CLIA-Certified Assay

Clinical outcomes were assessed in efficacy-evaluable patients with TMB ≥16 mut/Mb versus TMB ≥10 and <16 mut/Mb tumors by any CLIA-certified assay, including F1(CDx), in an exploratory analysis. Consistent with results from the F1(CDx) testing cohorts, in 56 patients with TMB ≥16 mut/Mb tumors by any CLIA-certified assay, confirmed ORR was 28.6% (16/56, including 3 CR and 13 PR; 95% CI, 17.3–42.2) and DCR was 55.4% (31/56; 95% CI, 41.5–68.7), compared with a confirmed ORR of 3.1% (2/64, both PR; 95% CI, 0.4–10.8) and DCR of 21.9% (14/64; 95% CI, 12.5–34.0) in 64 patients with TMB ≥10 and <16 mut/Mb tumors. Median treatment duration was 4.3 months (median of 6.5 cycles; range, 1–31) and 0.8 months (median of 2.0 cycles; range, 1–18), respectively (Supplementary Fig. S5A and S5B). Median PFS was 4.8 months (95% CI, 2.6–5.8) in patients with TMB ≥16 mut/Mb and 1.4 months (95% CI, 1.4–2.6) in those with TMB ≥10 and <16 mut/Mb tumors (Supplementary Fig. S6A), and median OS was 19.8 months (95% CI, 12.2–NE) and 8.5 months (95% CI, 5.2–14.9), respectively (Supplementary Fig. S6B).

Clinical Outcomes by MSI Status

MSI-H status enriches for response to immunotherapy and has previously been shown to correlate with TMB-H status (21). Among 86 efficacy-evaluable patients with F1(CDx) TMB ≥10 mut/Mb tumors and known MSI status, 11 had TMB ≥16 mut/Mb + MSI-H and 29 had TMB ≥16 mut/Mb + stable or low MSI (MSI-SL). The remaining 46 patients had TMB ≥10 and <16 mut/Mb tumors, of which all but one was MSI-SL.

In patients with TMB ≥16 mut/Mb tumors, objective responses were observed in both the MSI-H and MSI-SL subgroups (Supplementary Table S5). Confirmed ORR was 54.5% (6/11; 95% CI, 23.4–83.3) versus 31.0% (9/29; 95% CI, 15.3–50.8), respectively. Median PFS was 8.3 months (95% CI, 1.3–NE) versus 5.6 months (95% CI, 2.7–8.5), respectively, and median OS was not reached in the TMB ≥16 mut/Mb + MSI-H group versus 19.8 months (95% CI, 11.8–NE) for TMB ≥16 mut/Mb + MSI-SL (Supplementary Fig. S7A and S7B). Within the MSI-SL population, significantly longer PFS (HR, 0.33; 95% CI, 0.19–0.58; P < 0.0001) was observed for patients with F1(CDx) TMB ≥16 mut/Mb versus TMB ≥10 and <16 mut/Mb tumors. Similar results were observed in the population of patients with TMB by any CLIA-certified assay. A *post hoc* exploratory analysis of differentially mutated genes by TMB and MSI subgroups is shown in Supplementary Table S6.

Objective Responses by PD-L1 Expression Status

To assess whether PD-L1 expression levels were associated with altered response, a *post hoc* exploratory analysis was conducted by PD-L1 status in patients with F1(CDx) TMB ≥16 mut/Mb tumors and known PD-L1 tumor proportion scores (TPS; available for 26 of 42 patients) or combined positive scores (CPS; 23/42). Compared with patients with TMB ≥16 mut/Mb, the TMB ≥10 and <16 mut/Mb cohort had a higher proportion of patients with TPS or CPS scores <1 by IHC, and no patients with TPS or CPS scores ≥50 (Table 1). MSI and PD-L1 status groups in patients with F1(CDx) TMB ≥16 mut/Mb are shown in Supplementary Fig. S8A and S8B.

Among patients with F1(CDx) TMB ≥16 mut/Mb tumors, those with TPS scores of <1, ≥1 and <50, and ≥50 had confirmed ORRs of 33.3% (5/15), 40.0% (2/5), and 50.0% (3/6), respectively (Supplementary Table S7). In patients with CPS scores of <1, ≥16 and <50, and ≥50, confirmed ORR was 25.0% (1/4), 35.7% (5/14), and 40.0% (2/5), respectively. Of note, all responders with colorectal cancer and known PD-L1 status had TPS and CPS scores <50.

Clinical Outcomes by *POLE/POLD1* Mutation Status

To assess the impact of putative pathogenic mutations in the DNA proofreading genes DNA polymerase epsilon (*POLE*) and delta 1 (*POLD1*; ref. 22) on clinical outcomes, we performed a *post hoc* exploratory analysis on the 90 efficacy-evaluable patients with F1(CDx) TMB with versus without *POLE/POLD1* exonuclease domain mutations. Nine patients (five with TMB ≥16 mut/Mb and four with TMB ≥10 and <16 mut/Mb tumors) had *POLE/POLD1*-mutated tumors by F1(CDx) testing in this population. ORR in *POLE/POLD1*-mutated tumors was 22.2% (2/9) versus 18.5% (15/81) in tumors without *POLE/POLD1* mutations (P = 0.87). Among 42 patients with TMB ≥16 mut/Mb tumors, ORR was 40.0% (2/5) versus 37.8% (14/37) in patients with versus without *POLE/POLD1* mutations, respectively (P = 1).

Median PFS in patients without *POLE/POLD1* exonuclease domain mutations was 1.9 months in the TMB ≥10 and <16 mut/Mb cohort, versus 5.6 months for TMB ≥16 mut/Mb (HR, 0.36; 95% CI, 0.21–0.60; P < 0.001) and 5.7 months for patients with TMB ≥16 mut/Mb + *POLE/POLD1* mutations (HR, 0.38; 95% CI, 0.13–1.08; P = 0.07). Data for PFS and OS are shown in Supplementary Fig. S9A and S9B.

We also assessed the potential impact of all nonsynonymous *POLE/POLD1* mutations based on recent work suggesting that *POLE/POLD1* mutations outside of the exonuclease domain may also enrich for response to immunotherapy (23). ORR, PFS, and OS did not significantly differ in patients with TMB ≥16 mut/Mb tumors with versus without any *POLE/POLD1* mutation.

Objective Responses by Tumor Type

Data from the real-world Flatiron Health-Foundation Medicine Clinico-Genomic Database (FH-FMI CGDB) indicate that among 73,693 tumors tested for TMB by F1(CDx), 8.4%

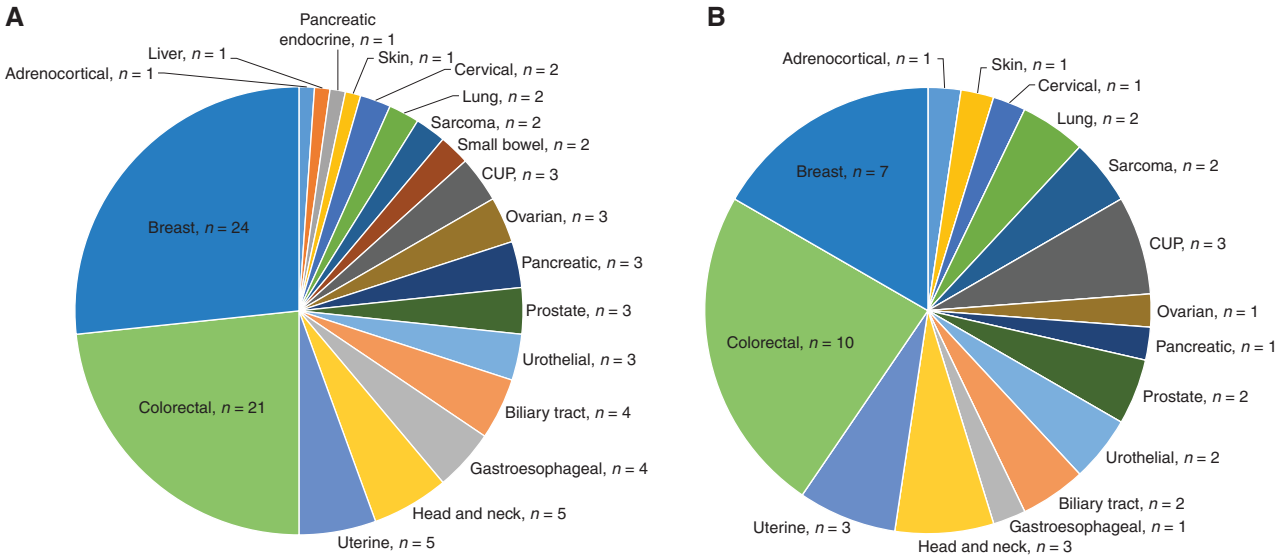

Figure 4. Tumor groups in efficacy-evaluable patients with F1(CDx) TMB. Tumor types from (**A**) all patients with F1(CDx) TMB ≥10 mut/Mb ($n = 90$) and (**B**) F1(CDx) TMB ≥16 mut/Mb ($n = 42$). Nineteen different tumor types for all patients with F1(CDx) TMB testing and 16 different tumor types for F1(CDx) TMB ≥16 mut/Mb were represented among efficacy-evaluable patients, with the largest groups comprised of patients with breast and colorectal cancers. CDx, Companion Diagnostic; CUP, carcinoma of unknown primary; F1, FoundationOne; TMB, tumor mutational burden.

are characterized as TMB ≥16 mut/Mb. Among the most common cancer types in the United States, TMB ≥16 mut/Mb was observed in 3.6% of breast, 3.1% of prostate, 16.3% of NSCLC, and 5.4% of colorectal tumors (Supplementary Table S8). TMB ≥16 mut/Mb was particularly prevalent in endometrial (15.8%) and bladder (16.4%) cancers, but was less common in pancreatic (0.8%) and ovarian (0.9%) cancers. Among tumors with stable MSI, 7.1% had TMB ≥16 mut/Mb.

In MyPathway, 19 different tumor types were included among all efficacy-evaluable patients with F1(CDx) TMB ≥10 mut/Mb tumors (Fig. 4A), and 16 tumor groups among those with F1(CDx) TMB ≥16 mut/Mb (Fig. 4B). The largest tumor groups overall were breast ($n = 24$) and colorectal ($n = 21$). Among 10 patients with colorectal cancer and F1(CDx) TMB ≥16 mut/Mb, confirmed responses were observed in seven patients (70.0%; 95% CI, 34.8–93.3; Table 2), of whom three had tumors characterized as MSI-H and three as MSI-SL. Only one of seven patients with F1(CDx) TMB ≥16 mut/Mb breast cancer had a response: a patient with hormone receptor–positive MSI-SL cancer. Of note, as five of the seven patients had hormone receptor–positive breast cancer, biological mechanisms other than TMB may be the primary drivers of tumor progression in these patients. In addition to the responses observed in colorectal and breast cancers, responses were reported in patients with F1(CDx) TMB ≥16 mut/Mb carcinomas of unknown primary (2/3), head and neck cancer (1/3), biliary tract cancer (1/2), and adrenocortical cancer (1/1); all responders in these groups had MSI-SL tumors. Responses were also observed in patients with F1(CDx) TMB ≥16 mut/Mb tumors in the pancreas (1/1), cervix (1/1), and prostate (1/2), of which the responders had MSI-H tumors. The single responder with a F1(CDx) TMB ≥10 and <16 mut/Mb tumor had biliary tract cancer (MSI status unknown; Supplementary Table S9).

Similar outcomes were observed in the full patient population with TMB by any CLIA-certified assay encompassing 20 different tumor types (Supplementary Fig. S10), with confirmed responses observed for patients with any CLIA-certified TMB ≥16 mut/Mb colorectal cancer (7/11), breast cancer (1/12), carcinoma of unknown primary (2/3), biliary tract cancer (1/3), cervical cancer (1/3), head and neck cancer (1/3), prostate cancer (1/3), adrenocortical cancer (1/1), and pancreatic cancer (1/1; Supplementary Table S10). Additionally, two patients with any CLIA-certified TMB ≥10 and <16 mut/Mb biliary tract cancer had a response (2/3).

CRs were observed in patients with primary orbital squamous cell carcinoma (MSI-SL; DOR 17.9 months, ongoing at data cutoff), biliary cancer (MSI-SL; DOR 15.5 months, ongoing; Supplementary Fig. S11A and S11B), and colon cancer (MSI-H; DOR 4.1 months). All three patients had TMB ≥16 mut/Mb by both any CLIA-certified assay and F1(CDx) testing.

Safety

Among the 121 treated patients, 90.9% (110/121) experienced a treatment-emergent adverse event (TEAE), including grade 3–5 TEAEs in 47.9% (58/121) and serious TEAEs in 33.1% (40/121) of patients. Treatment-related TEAEs were reported in 56.2% (68/121) of patients, most commonly fatigue (12.4%), pruritus (10.7%), and nausea (9.9%; Supplementary Table S11). Grade 3–4 related TEAEs were observed in 12.4% (15/121) of patients, most commonly hyponatremia and decreased lymphocyte count (each in 2.5% of patients), and related serious TEAEs in 6.6% (8/121). TEAEs led to study drug interruption in 19.0% (23/121) of patients, withdrawal from study drug in 5.0% (6/121), and death in 4.1% (5/121; none related to the study drug). No patients had a study drug reduction due to TEAEs.

Table 2. Clinical outcomes by tumor type in patients with F1(CDx) TMB ≥16 mut/Mb tumors (*n* = 42)

Tumor type	*n*	ORR, *n* (%) 95% CI	Responses by MSI and *POLE/POLD1* status[a]					PFS, median months 95% CI
			MSI-H + *POLE/POLD1* mutated, *n/n*	MSI-H + *POLE/POLD1* MND, *n/n*	MSI-SL + *POLE/POLD1* mutated, *n/n*	MSI-SL + *POLE/POLD1* MND, *n/n*	MSI status unknown + *POLE/POLD1* MND, *n/n*	
Overall	42	16 (38.1) 23.6–54.4	0/1	6[b]/10	2/4	7[c]/25	1/2	5.7 2.7–8.5
Colorectal	10	7 (70.0) 34.8–93.3	—	3[b]/4	1/1	2/4	1/1	11.1 5.5–NE
Breast	7	1 (14.3) 0.4–57.9	—	—	0/1	1/6	—	1.4 1.2–9.7
Carcinoma of unknown primary	3	2 (66.7) 9.4–99.2	0/1	—	1/1	1/1	—	4.8 1.3–5.7
Head and neck	3	1 (33.3) 0.8–90.6	—	—	—	1[b]/3	—	5.7 1.2–NE
Uterine	3	0	—	0/2	—	0/1	—	1.3 1.3–1.3
Biliary tract	2	1 (50.0) 1.3–98.7	—	—	—	1[b]/2	—	NE 8.5–NE
Lung	2	0	—	—	0/1	0/1	—	7.9 5.8–9.9
Prostate	2	1 (50.0) 1.3–98.7	—	1/1	—	0/1	—	8.4 8.3–8.5
Sarcoma	2	0	—	—	—	0/2	—	NE NE–NE
Urothelial	2	0	—	—	—	0/2	—	3.2 0.9–5.5
Adrenocortical	1	1 (100) 2.5–100.0	—	—	—	1/1	—	NE NE–NE
Cervical	1	1 (100) 2.5–100.0	-	1/1	—	—	—	NE NE–NE
Gastroesophageal	1	0	—	0/1	—	—	—	4.1 NE–NE
Ovarian	1	0	—	—	—	—	0/1	1.3 NE–NE
Pancreatic	1	1 (100) 2.5–100.0	—	1/1	—	—	—	NE NE–NE
Skin	1	0	—	—	—	0/1	—	2.7 NE–NE

Abbreviations: CDx, Companion Diagnostic; CI, confidence interval; ORR, objective response rate; CR, complete response; F1, FoundationOne; MND, mutation not detected; NA, not applicable; NE, not estimable; PFS, progression-free survival.

[a]*POLE/POLD1* mutations refer to mutations in the exonuclease domains only.

[b]One responder had a CR.

[c]Two responders had a CR.

DISCUSSION

Data from MyPathway indicate that atezolizumab treatment of tumors with TMB ≥16 mut/Mb had promising, durable clinical activity across a variety of advanced solid tumor types. Notably, patients in this analysis had a median of three prior lines of therapy and no suitable alternative treatment options at enrollment. Patients with F1(CDx) TMB ≥16 mut/Mb tumors achieved a confirmed ORR of 38.1% (95% CI, 23.6–54.4), including three CRs, and a DCR of 61.9% (95% CI, 45.6–76.4). In contrast, patients with TMB ≥10 and <16 mut/Mb tumors had a significantly lower ORR of 2.1% (95% CI, 0.1–11.1) and DCR of 22.9% (95% CI, 12.0–37.3). Median PFS was 5.7 months and 1.8 months in patients with TMB ≥16 mut/Mb versus TMB ≥10 and <16 mut/Mb tumors, respectively, and median OS was 19.8 months and 11.4 months. These results suggest that in our tissue-agnostic tumor population, response to atezolizumab was enriched in tumors with TMB ≥16 mut/Mb, with limited activity observed in tumors with TMB <16 mut/Mb.

As of October 2021, National Comprehensive Cancer Network (NCCN) guidelines for 15 different tumor types recommended assessment or consideration of assessment for TMB-H status for certain patients as a strategy for treatment determination (24–38). A recent retrospective analysis in a large population suggested that a TMB cutoff of ≥10 mut/Mb is predictive for response to checkpoint inhibitors only in cancer types where CD8 T-cell levels correlate with neoantigen load (10). McGrail and colleagues reported notable response rates against melanoma, lung cancer, and bladder cancer, with a trend toward increased response in colorectal cancer, but activity was limited for breast cancer, prostate cancer, and glioma (10). Based on data from KEYNOTE-158, pembrolizumab received accelerated FDA approval for unresectable or metastatic solid tumors of any type with TMB ≥10 mut/Mb in patients lacking satisfactory alternative treatment options (7, 8). However, enrollment in KEYNOTE-158 was restricted to 10 tumor types (8). These included TMB-H tumors previously shown to be sensitive to immunotherapy, such as small-cell lung cancer (3), and excluded colorectal and breast cancers. In contrast, eligibility for the prospective MyPathway study was based on tumor molecular characteristics, regardless of tumor location. Among the 121 patients included in this analysis, 20 different tumor groups were assessed, with responses observed in nine tumor types. Particularly high response rates were reported in patients with colorectal cancer [70.0% in 10 patients with F1(CDx) TMB ≥16 mut/Mb tumors, including responses in both MSI-H and MSI-SL tumors]. However, among seven patients with F1(CDx) TMB ≥16 mut/Mb breast cancer, only one response was observed. The divergent results observed for colorectal and breast cancers were generally consistent with the data reported by McGrail and colleagues (10). Responses were also observed in patients with head and neck, biliary tract, prostate, adrenocortical, cervical, and pancreatic cancers, as well as carcinomas of unknown primary in our analysis. These results are encouraging for patients with a spectrum of tumor types characterized by elevated TMB status, including rare and difficult-to-treat tumors. Further prospective work will be needed to refine the biological characteristics of likely responders and to study differences between the activity of PD-1– and PD-L1–targeting agents within the TMB-H pan-tumor population.

As MSI-H status has been shown to correlate with TMB-H in several cancer types, including colorectal and endometrial cancers (21), we wanted to determine whether atezolizumab had clinical activity in our analysis beyond the presence of MSI-H tumor status. Consistent with previous reports for checkpoint blockade in patients with MSI-H tumors (21, 39), ORR and DCR were numerically higher for MSI-H versus MSI-SL tumors (ORR: 54.5% vs. 31.0%, respectively, and DCR: 72.7% vs. 58.6%) within the F1(CDx) TMB ≥16 mut/Mb population. We observed meaningful activity in a variety of tumor types regardless of MSI status, suggesting that MSI-H is not the only driver of response to atezolizumab in patients with TMB-H tumors. These data align with recent analyses suggesting that TMB-H is an independent biomarker for response to PD-1/PD-L1 inhibitors in MSI-H colorectal cancer (40).

Prior studies have suggested that PD-L1 expression has limitations as a tumor-agnostic predictive biomarker for response to immune-checkpoint inhibitors (41, 42). Although universal guidelines for assessing or scoring PD-L1 expression are lacking, reports of response to anti–PD-1 or anti–PD-L1 therapy in patients with low PD-L1 expression suggest that other tumor molecular characteristics may influence response to atezolizumab (41, 42). In an exploratory analysis in MyPathway, objective responses were observed in patients with TMB ≥16 mut/Mb in all PD-L1 expression level groups. However, we observed that ORR numerically increased with higher PD-L1 TPS and CPS scores, and among the three patients with CR in the overall analysis, two had TPS and CPS scores >50. As with MSI status, TMB ≥16 mut/Mb may enrich for response regardless of PD-L1 expression level (2).

Other biomarkers of interest include mutations in *POLE*/*POLD1*, which can lead to deficient DNA repair and tumor hypermutation, potentially resulting in sensitivity to checkpoint inhibitors (23). A recent retrospective analysis indicated that checkpoint inhibitors improved OS in patients with TMB ≥10 mut/Mb versus TMB <10 mut/Mb colorectal cancer, but the predictive value of TMB status disappeared when patients with *POLE*/*POLD1* mutations or deficient mismatch repair were omitted (11). In our exploratory analysis of patients without *POLE*/*POLD1* exonuclease domain-mutated tumors, median PFS, but not OS, was significantly longer in those with TMB ≥16 mut/Mb compared with TMB ≥10 and <16 mut/Mb. Among patients with TMB ≥16 mut/Mb tumors, ORR and median PFS were similar between patients with versus without *POLE*/*POLD1*-mutated tumors (ORR: 40.0% vs. 37.8%, PFS: 5.7 vs. 5.6 months). Notably, seven responders (including two with CR) were observed among 25 patients with TMB ≥16 mut/Mb + MSI-SL + nonmutated *POLE*/*POLD1* tumors, suggesting that MSI-H status and *POLE*/*POLD1* mutations are not sufficient to account for responses in patients with TMB ≥16 mut/Mb tumors. Additional prospective research will be needed to further refine how *POLE*/*POLD1* mutations and other tumor hypermutation–associated biomarkers affect response in patients with TMB ≥16 mut/Mb tumors treated with immunotherapy.

The selection of centralized TMB testing via F1(CDx) for the primary efficacy endpoint was based on the known

presence of variability between assays for TMB (19, 20). FoundationOne CDx is currently the only FDA-approved companion diagnostic for TMB. Prior studies have indicated that the FoundationOne comprehensive genomic profiling assay provides an accurate assessment of whole-exome TMB (5). In contrast, the ability to accurately estimate TMB may be limited in smaller gene panels, which may overestimate TMB (19, 43). We observed some incidences of discordance between central and local TMB testing results, including 17 patients who were enrolled based on locally tested TMB ≥10 mut/Mb tumors, but had TMB <10 mut/Mb from central F1(CDx) retesting. Some of these discrepancies may be attributed to differences in the time points of tissue collection and/or site heterogeneity of the tissue samples (44). However, our data suggested that regardless of the type of TMB assay, atezolizumab consistently appeared to have promising activity in the cohort of patients with TMB ≥16 mut/Mb tumors, with very limited activity observed in tumors with TMB <16 mut/Mb.

Although recent studies have suggested limited predictive power of TMB for response to immunotherapy in pan-tumor populations (10, 11), identification of a TMB cutoff that maximizes efficacy while avoiding unnecessary toxicities could be particularly valuable for the treatment of tumors of unknown primary or rare tumor types that may not have tumor-specific indications. Of note, the analysis by McGrail and colleagues was based on TMB derived from *in silico* analysis across various methods, and approximated TMB-H based on a cutoff of 10 mut/Mb for a FoundationOne CDx panel (rather than empirical measurements from FoundationOne CDx testing), an approach that may require further validation and may limit the comparability of findings (10). In the retrospective study of atezolizumab by Shemesh and colleagues, the TMB cutoff of 16 mut/Mb was based on a balance between high response rate and reasonable prevalence across a variety of tumor types (17). Our prespecified primary analysis population of patients with TMB ≥16 mut/Mb encompassed the majority of responders across multiple tumor types, although we observed continued enrichment for response with TMB cutoffs higher than 16 mut/Mb, consistent with prior studies (17, 45). Our results align with the designation of TMB 10–15 mut/Mb as an "equivocal zone" for response to checkpoint inhibitors by the TMB Harmonization Project working group (https://www.focr.org/sites/default/files/Tissue-Agnostic-TMB_Summary.pdf). Although our data support a TMB threshold of 16 mut/Mb as an appropriate stratification for patients who are likely or unlikely to respond to atezolizumab treatment based on TMB status, we cannot be certain of the negative predictive value of TMB <16 mut/Mb due to the small sample size. Further studies will be necessary to determine whether a different cutoff would be more appropriate, and to consider additional factors such as tumor type and biomarker profile to potentially increase the predictive value of TMB (10, 11).

This analysis was limited by the lack of a control arm or patient randomization, the use of nonblinded investigator assessments for tumor response, small patient cohorts in some subgroup analyses, and the use of local TMB testing for the enrollment of an analysis primarily based on F1(CDx) TMB. In particular, as patients with TMB <10 mut/Mb tumors were not permitted in the study, this analysis omitted patients who may have had a local assessment of TMB <10 mut/Mb and central assessment of TMB ≥10 mut/Mb, potentially biasing the classification of patients around the F1(CDx) TMB 16 mut/Mb cutoff. Finally, as patients with tumors already indicated for treatment with immunotherapy at the time of study start or who had progressed on prior immunotherapy were not included in this analysis, efficacy in this patient group is unknown.

Our analysis from MyPathway suggests that TMB ≥16 mut/Mb determined by F1(CDx), an FDA-approved assay for TMB in solid tumors, enriches for response to atezolizumab monotherapy in a tumor-agnostic setting. These data support atezolizumab as a potential treatment option across a broad spectrum of tumor types with TMB ≥16 mut/Mb, including patients with rare cancers lacking other treatment choices and those with cancers of unknown primary origin, and add to the growing body of evidence demonstrating activity for agents targeting PD-1 and PD-L1 in advanced TMB-H solid tumors. To further improve the selection of patients likely to respond to atezolizumab treatment, future studies should explore additional molecular markers in TMB-H tumors that may influence response; other TMB cutoffs, including suitable TMB cutoffs in the population of patients with prior immunotherapy; and the activity of combination therapies with atezolizumab. Another consideration for the future may be the utilization of PD-1– and PD-L1–targeting agents earlier in the treatment course, or even perhaps in the adjuvant setting. This approach has demonstrated activity in stage II/III malignant melanoma (46–48) and NSCLC (49) and is being explored in MSI-H endometrial and colorectal cancers. The omission or delay of chemotherapy for these patients would mark a significant paradigm shift in the treatment of advanced solid tumors.

METHODS

Study Design and Participants

MyPathway (NCT02091141) is an open-label, multicenter, nonrandomized, multiple basket phase IIa trial. Eligible patients have previously treated advanced solid tumors with potentially actionable molecular alterations (Supplementary Fig. S1). In this cohort analysis, patients were ≥18 years old and had histologically documented tumors with TMB ≥10 mut/Mb, as determined by any CLIA-certified assay; measurable disease by RECIST v1.1 (50); an Eastern Cooperative Oncology Group performance status score of 0 or 1; and adequate renal and liver function. Patients with prior cancer immunotherapy treatment, concurrent anticancer therapies, hematologic cancers, or uncontrolled central nervous system metastasis were excluded. Patients were not eligible if they had a tumor type already indicated for FDA-approved treatment with the study drug, or another suitable therapy option that could convey clinical benefit per the treating physician's judgment. Full inclusion and exclusion criteria are available in the online protocol (MyPathway Protocol v9_Redacted).

Atezolizumab 1200 mg was administered intravenously every 3 weeks until disease progression or unacceptable toxicity. In patients included in this analysis, tumors were assessed by the investigator per RECIST v1.1 at baseline and every two treatment cycles (every 6 weeks) for the first 24 weeks, and then every four treatment cycles (every 12 weeks) thereafter. Adverse events occurring from the first treatment until 90 days after the last dose of study treatment were assessed by the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Although the MyPathway atezolizumab arm opened on February 6, 2017 (protocol version 4), as a signal-seeking cohort, enrollment and safety/efficacy assessment criteria for this arm were amended for registrational intent as of August 29, 2018 (protocol version 6). As such, the analysis reported here includes only patients enrolled per protocol versions 6 and beyond. Methods for the exploratory analysis of patients enrolled per protocol versions 4 and 5 are described in the Supplementary Appendix.

MyPathway is conducted in accordance with the International Conference on Harmonization guideline for Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by the institutional review board/ethics committee at each trial center. All patients provided written informed consent to participate in the study.

Molecular Assessments

Patients were enrolled based on TMB ≥10 mut/Mb tumors from any TMB assay performed in a CLIA-certified laboratory using the most recent tumor biopsy, if available. Patients without testing results from the most recent biopsy could be enrolled based on available molecular testing results if all eligibility criteria were otherwise fulfilled. Due to known variability in TMB measurements between different gene panels (19, 20), patients who enrolled based on TMB results assessed by CLIA-certified assays other than FoundationOne or FoundationOne CDx (Foundation Medicine; ref. 51) were required to provide tissue samples for central retesting by F1(CDx) for the primary analysis. Incidence of tumors by TMB cutoff level and tumor type was determined using real-world data from F1(CDx) testing in the FH-FMI CGDB; additional details are shown in the Supplementary Appendix.

MSI status and *POLE*/*POLD1* status were determined by central F1(CDx) testing, or by a local test result as provided in the molecular profiling report from next-generation sequencing assays that included MSI or *POLE*/*POLD1* as biomarkers. PD-L1 CPS and TPS scores were determined by IHC using central testing of archival tissue samples (PD-L1 IHC 22C3 pharmDx assay; Dako). In the absence of tissue available for central PD-L1 testing, locally assessed TPS scores were also permitted if performed using the PD-L1 IHC 22C3 pharmDx assay. Analyses of genes with differential mutation rates between TMB and MSI subgroups were based on F1(CDx) testing data.

Endpoints

The preplanned primary efficacy endpoint was ORR per RECIST v1.1 criteria in the cohort of patients with TMB ≥16 mut/Mb tumors, as assessed by F1(CDx) testing. This threshold was defined based on data from a large, retrospective analysis of atezolizumab monotherapy that indicated TMB ≥16 mut/Mb is associated with improved ORR and DOR in patients with various solid tumor types treated with atezolizumab (17). Response was also evaluated in patients with TMB ≥10 and <16 mut/Mb tumors by F1(CDx). Patients were assessed by the investigator until the last patient in the study ended treatment, at which point scans would be submitted for independent central review, as prespecified in the study protocol. As some patients were still on treatment by the data cutoff, investigator-assessed objective responses are reported in the current analysis.

Secondary efficacy endpoints included DCR, DOR, PFS, and OS. Additional analyses were performed in subgroups of patients with TMB ≥16 mut/Mb or TMB ≥10 and <16 mut/Mb by any CLIA-certified assay [including patients with F1(CDx) testing results]. Safety and tolerability were assessed in all patients who received at least one dose of study treatment. Prespecified exploratory endpoints included correlation of MSI status with clinical outcomes. Analyses of clinical outcomes by PD-L1 and *POLE*/*POLD1* status and differential mutation analyses were *post hoc* and exploratory.

Statistical Analysis

The efficacy analysis population was comprised of patients treated and evaluated for efficacy, or who discontinued treatment for any reason prior to the first post-baseline tumor assessment. Confirmed investigator-assessed best overall responses were used to calculate ORR (defined as the percentage of patients with CR or PR). Confirmatory responses were not required for the calculation of DCR (defined as the percentage of patients with CR, PR, or SD >4 months). DOR was calculated as time from notation of first response to PD or death, or to the last tumor assessment if there was no PD or death. PFS was calculated as time from first treatment to PD or death, or to the last tumor assessment if there was no PD or death. OS was calculated as time from first treatment to death, or last date known to be alive if there was no death. ORR 95% CIs were calculated by the Clopper–Pearson estimation method. Median PFS, OS, and DOR and their 95% CIs were estimated by the Brookmeyer–Crowley method. The difference in ORR between TMB ≥16 mut/Mb versus ≥10 and <16 mut/Mb and *POLE*/*POLD1* subgroups was assessed by the Boschloo unconditional exact test (52), and the association of *POLE*/*POLD1* mutations with TMB was calculated using the Wilcoxon test. The statistical analysis for association of ORR with F1(CDx) TMB cutoff was based on a marginal structural model estimate for ORR at various TMB cutoffs (53). Enrichment for differential mutation rates in the gene analysis were calculated using Chi square or Fisher exact test, and P_{adj} values were based on the Benjamini–Hochberg method. Methods for estimated confirmed ORR adjusted by prior number of lines of therapy and gender are described in the Supplementary Appendix.

Data Availability Statement

For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see https://go.roche.com/data_sharing. Qualified researchers may request access to deidentified patient-level data and clinical study documentation via the following link: http://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing/clinical_study_documents_request_form.htm

Anonymized records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient reidentification.

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Authors' Disclosures

C.F. Friedman reports other support from Genentech/Roche during the conduct of the study, as well as personal fees from Arch Oncology and Bristol Myers Squibb, and other support from Merck outside the submitted work. J.D. Hainsworth reports other support from Genentech during the conduct of the study. R. Kurzrock has received research funding from Biological Dynamics, Boehringer Ingelheim, Debiopharm, Foundation Medicine, Genentech, Grifols, Guardant, Incyte, Konica Minolta, MedImmune, Merck Serono, Omniseq, Pfizer, Sequenom, Takeda, and TopAlliance, and is a consultant/advisory board member for and/or has received speaker fees from for Actuate Therapeutics, AstraZeneca, Bicara Therapeutics, Biological Dynamics, EISAI, EOM Pharmaceuticals, Iylon, Merck, NeoGenomics, Neomed, Pfizer, Prosperdtx, Roche, TD2/Volastra, Turning Point Therapeutics, and Xbiotech outside the submitted work; has an equity interest in CureMatch Inc., CureMetrix, and IDbyDNA; and serves on the Board of CureMatch and CureMetrix, and is a cofounder of CureMatch. D.R. Spigel reports grants and

other support from Novocure, Pfizer, Genentech/Roche, Novartis, Bristol Myers Squibb, AstraZeneca, EMD Serono, GlaxoSmithKline, Janssen, Lily, and Molecular Templates, grants from Aeglea Biotherapeutics, Agios, Apollomics, Arcus, Arry Therapeutics, Astellas, Bayer, BeiGene, BIND Therapeutics, BioNTech RNA, Blueprint Medicines, Boehringer Ingelheim, Calithera, Celgene, Celldex, Clovis, Cyteir Therapeutics, Daiichi Sankyo, Denovo Biopharma, Eisai, Elevation Oncology, Evelo Biosciences, G1Therapeutics, GRAIL, Hutchinson MediPharma, ImClone Systems, Incyte, ImmunoGen, Ipsen, Kronos Bio, Loxo Oncology, MarcoGenics, MedImmune, Merck, Molecular Partners, Nektar, Neon Therapeutics, Oncologie, PTC Therapeutics, Pure Tech Health, Razor Genomics, Repare Therapeutics, Rgenix, Tizona Therapeutics, and Verastem, and other support from Amgen, Curio Sciences, Evidera, Exelixis, Intellisphere, Ipsen Biopharma, Jazz Pharmaceuticals, Mirati Therapeutics, Puma Biotechnology, Regeneron Pharmaceuticals, and Sanofi-Aventis outside the submitted work. H.A. Burris reports grants from Genentech/Roche during the conduct of the study, as well as other support from HCA Healthcare/Sarah Cannon, Daiichi Sankyo, Pfizer, Bayer, GRAIL, Novartis, Vincerx Pharma, AstraZeneca, and Incyte and grants from Bristol Myers Squibb, Incyte, AstraZeneca, MedImmune, Macrogenics, Novartis, Boehringer Ingelheim, Lilly, Seattle Genetics, Merck, Agios, Jounce Therapeutics, Moderna Therapeutics, CytomX Therapeutics, GlaxoSmithKline, Verastem, Tesaro, BioMed Valley Discoveries, TG Therapeutics, Vertex, eFFECTOR Therapeutics, Janssen, Gilead Sciences, BioAtla, CicloMed, Harpoon Therapeutics, Arch, Arvinas, Revolution Medicines, Array BioPharma, Bayer, BIND Therapeutics, Kymab, miRNA Therapeutics, Pfizer, Takeda/Millennium, Foundation Medicine, EMD Serono, ARMO BioSciences, CALGB, Hengrui Therapeutics, Infinity Pharmaceuticals, XBiotech, Zymeworks, Coordination Pharmaceuticals, NGM Biopharmaceuticals, Gossamer Bio, Ryvu Therapeutics, BioTheryX, and AbbVie outside the submitted work. C.J. Sweeney reports personal fees from Lilly and grants and personal fees from Bayer, Sanofi, Pfizer, Astellas, Janssen, and Genentech during the conduct of the study, as well as a patent for KDM5D and ZFP36 issued, a patent for cabozantinib and abiraterone in prostate cancer issued, and a patent for parthenolide in cancer issued. F. Meric-Bernstam reports grants and personal fees from F. Hoffmann-La Roche/Genentech during the conduct of the study, as well as personal fees from AbbVie, Aduro BioTech Inc., Alkermes, AstraZeneca, DebioPharm, eFFECTOR Therapeutics, IBM Watson, Infinity Pharmaceuticals, The Jackson Laboratory, Kolon Life Science, Lengo Therapeutics, OrigiMed, PACT Pharma, Parexel International, Pfizer Inc., Samsung Bioepis, Seattle Genetics Inc., Tallac Therapeutics, Tyra Biosciences, Xencor, Zymeworks, Black Diamond, Biovica, Eisai, Immunomedics, Inflection Biosciences, Karyopharm Therapeutics, Loxo Oncology, Mersana Therapeutics, OnCusp Therapeutics, Puma Biotechnology Inc., Silverback Therapeutics, Spectrum Pharmaceuticals, and Zentalis and grants from Aileron Therapeutics, Inc., AstraZeneca, Bayer Healthcare Pharmaceutical, Calithera Biosciences Inc., Curis Inc., CytomX Therapeutics Inc., Daiichi Sankyo Co. Ltd., Debiopharm International, eFFECTOR Therapeutics, Guardant Health Inc., Klus Pharma, Takeda Pharmaceutical, Novartis, Puma Biotechnology Inc., and Taiho Pharmaceutical Co. outside the submitted work. Y. Wang reports other support from Genentech Inc. during the conduct of the study, as well as other support from Genentech Inc. outside the submitted work. J. Levy reports other support from Genentech Inc. during the conduct of the study, as well as other support from Genentech Inc. outside the submitted work. J. Grindheim reports other support from Genentech Inc. during the conduct of the study, as well as other support from Genentech Inc. outside the submitted work. D.S. Shames reports other support from Genentech outside the submitted work; is listed as an inventor on multiple patent applications pending related to the current study; and is an employee of Genentech and owns stock in Roche Holdings. K. Schulze reports other support from Genentech Inc. during the conduct of the study, as well as other support from Genentech Inc. outside the submitted work. C. Swanton reports personal fees from Roche-Genentech during the conduct of the study; grants from Boehringer Ingelheim and Invitae (formerly Archer Dx), grants and personal fees from Pfizer, Roche-Ventana, AstraZeneca, Bristol Myers Squibb, and Ono Pharmaceutical, personal fees from Amgen, Novartis, GlaxoSmithKline, Illumina, Genentech, MSD, Bicycle Therapeutics, Medicxi, Sarah Cannon Research Institute, Metabomed, and Roche Shanghai, other support from Apogen Biotech and Epic Bioscience, and personal fees and other support from GRAIL and Achilles Therapeutics outside the submitted work; and a patent for assay technology to detect tumor recurrence (PCT/GB2017/053289) issued, a patent for targeting neoantigens (PCT/EP2016/059401) issued, a patent for identifying patient response to immune-checkpoint blockade (PCT/EP2016/071471) issued, a patent for determining HLA LOH (PCT/GB2018/052004) issued, a patent for predicting survival rates of patients with cancer (PCT/GB2020/050221) issued, a patent for treating cancer by targeting insertion/deletion mutations (PCT/GB2018/051893) issued, a patent for identifying insertion/deletion mutation targets (PCT/GB2018/051892) issued, a patent for methods for lung cancer detection (PCT/US2017/028013) issued, and a patent for identifying responders to cancer treatment (PCT/GB2018/051912) issued. No disclosures were reported by the other authors.

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C.F. Friedman: Investigation, writing–original draft, writing–review and editing. **J.D. Hainsworth:** Conceptualization, investigation, methodology, writing–review and editing. **R. Kurzrock:** Conceptualization, investigation, methodology, writing–review and editing. **D.R. Spigel:** Conceptualization, investigation, methodology, writing–review and editing. **H.A. Burris:** Conceptualization, investigation, methodology, writing–review and editing. **C.J. Sweeney:** Conceptualization, investigation, methodology, writing–review and editing. **F. Meric-Bernstam:** Conceptualization, investigation, methodology, writing–review and editing. **Y. Wang:** Conceptualization, data curation, software, formal analysis, investigation, methodology, writing–review and editing. **J. Levy:** Conceptualization, data curation, software, formal analysis, investigation, methodology, writing–review and editing. **J. Grindheim:** Formal analysis, methodology, writing–review and editing. **D.S. Shames:** Conceptualization, data curation, investigation, methodology, writing–review and editing. **K. Schulze:** Conceptualization, data curation, investigation, methodology, writing–review and editing. **A. Patel:** Conceptualization, data curation, supervision, investigation, methodology, project administration, writing–review and editing. **C. Swanton:** Conceptualization, investigation, methodology, writing–review and editing.

Acknowledgments

The authors are grateful to the patients, families, and study teams who participated in MyPathway. We would also like to thank Julia Malato (Genentech) for biosample management support. The MyPathway study was funded by F. Hoffmann-La Roche/Genentech. Medical writing support was provided by Sabrina Hom, PhD, of Ashfield MedComms, an Ashfield Health Company, and was funded by F. Hoffmann-La Roche/Genentech. C.F. Friedman was supported in part by the NIH/NCI Cancer Center Support Grant P30 CA008748.

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Received April 13, 2021; revised October 15, 2021; accepted December 2, 2021; published first December 7, 2021.

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