

Targeted Therapy for Advanced Solid Tumors on the Basis of Molecular Profiles: Results From MyPathway, an Open-Label, Phase IIa Multiple Basket Study

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ABSTRACT

Purpose

Detection of specific molecular alterations in tumors guides the selection of effective targeted treatment of patients with several types of cancer. These molecular alterations may occur in other tumor types for which the efficacy of targeted therapy remains unclear. The MyPathway study evaluates the efficacy and safety of selected targeted therapies in tumor types that harbor relevant genetic alterations but are outside of current labeling for these treatments.

Methods

MyPathway (ClinicalTrials.gov identifier: NCT02091141) is a multicenter, nonrandomized, phase IIa multiple basket study. Patients with advanced refractory solid tumors harboring molecular alterations in human epidermal growth factor receptor-2, epidermal growth factor receptor, v-raf murine sarcoma viral oncogene homolog B1, or the Hedgehog pathway are treated with pertuzumab plus trastuzumab, erlotinib, vemurafenib, or vismodegib, respectively. The primary end point is investigator-assessed objective response rate within each tumor-pathway cohort.

Results

Between April 1, 2014 and November 1, 2016, 251 patients with 35 different tumor types received study treatment. The efficacy population contains 230 treated patients who were evaluated for response or discontinued treatment before evaluation. Fifty-two patients (23%) with 14 different tumor types had objective responses (complete, n = 4; partial, n = 48). Tumor-pathway cohorts with notable objective response rates included human epidermal growth factor receptor-2–amplified/overexpressing colorectal (38% [14 of 37]; 95% CI, 23% to 55%) and v-raf murine sarcoma viral oncogene homolog B1 V600-mutated non–small-cell lung cancer (43% [six of 14]; 95% CI, 18% to 71%).

Conclusion

The four currently approved targeted therapy regimens in the MyPathway study produced meaningful responses when administered without chemotherapy in several refractory solid tumor types not currently labeled for these agents.

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INTRODUCTION

Molecular profiling is routinely used to guide the selection of targeted therapies for the treatment of patients with lung, breast, colon, and other types of cancer. When used in molecularly identified patients with indicated tumor types, agents targeting human epidermal growth factor receptor-2 (HER2),¹ epidermal growth factor receptor (EGFR),² v-raf murine sarcoma viral oncogene homolog B1 (BRAF),³ and the Hedgehog pathway⁴ have been among the most effective therapies introduced during the last 20 years.

Molecular alterations in these genes and pathways also occur in a variety of nonindicated tumor types. The low incidence of the targeted molecular alterations in these tumor types (usually < 5%) has made it difficult to recruit sufficient numbers of patients into traditional drug development studies, although activity has been documented in anecdotal reports.⁵⁻¹²

Basket studies provide the opportunity to evaluate the efficacy of targeted therapies in patient populations defined by the presence of specific molecular tumor abnormalities, rather than by primary site or tumor histology.^{13,14} Results of

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ASSOCIATED CONTENT



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several small basket studies have recently been reported. In one such study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01524978) identifier: NCT01524978), treatment with vemurafenib produced responses in 24 of 95 patients (25%) with *BRAF* V600-mutated tumor types other than melanoma and colorectal cancer.¹⁵ Such data suggest that certain molecular alterations are important in determining the response to targeted treatment, independent of tumor type.¹⁶ However, multiple variables influence the efficacy of targeted therapy, including the biology and relevance of the target, the mechanism of target inhibition, the tumor type, the presence of other molecular alterations, and the therapy selected.

MyPathway is an ongoing, multicenter, phase IIa study that combines multiple basket studies under an adaptable master protocol. The objective of the study is to evaluate the efficacy of treatments targeting molecular alterations in HER2 (pertuzumab plus trastuzumab), *BRAF* (vemurafenib), Hedgehog pathway (vismodegib), or EGFR (erlotinib) in patients with tumor types outside of current labeling for these treatment regimens. In this report, we summarize the efficacy results in the first 230 treated patients who were efficacy evaluable.

METHODS

Patients

Eligible patients are required to have refractory, metastatic solid tumors containing targetable, pathway-activating, molecular alterations in HER2, EGFR, *BRAF*, or the Hedgehog pathway. Molecular profiling was not conducted as part of this study; rather, eligible patients were required to have previous profiling demonstrating one of the target alterations. Molecular testing by various local Clinical Laboratory Improvement Amendments (CLIA)-approved laboratories was acceptable in this study. Molecular profiling must have been performed on tissue obtained at the most recent tumor biopsy.

Additional eligibility requirements include measurable or evaluable lesions¹⁷ and an Eastern Cooperative Oncology Group performance status score of 0, 1, or 2. Patients with tumor types for which the study treatments are approved or in active development are not eligible. Specific tumor mutations with evidence suggesting inactivity of the study drugs are also ineligible. All patients also need to fulfill additional eligibility criteria pertinent to the specific therapeutic agents (Data Supplement).

Molecular alterations eligible for MyPathway as well as required testing methods are detailed in [Table 1](#). Tumors with HER2 amplification, overexpression, and/or activating mutations were eligible. For EGFR and *BRAF*, known or putative activating mutations were required. Eligible Hedgehog pathway alterations included gain-of-function mutations of Smoothened (*SMO*) or loss-of-function mutations of Patched Homolog-1 (*PTCH-1*). Unusual mutations considered possible activating mutations for any of the pathways (or loss of function mutations for *PTCH-1*) were permitted if previously reported in at least two unique specimens in the Catalogue of Somatic Mutations in Cancer database.⁶

The above protocol-specified molecular alterations were identified through local CLIA-approved laboratory reports and reviewed by the study medical monitor for eligibility. For unusual molecular alterations, the medical monitor consulted appropriate members of the MyPathway Steering Committee regarding eligibility. Scanned laboratory reports are kept in a separate database from clinical trial data.

Trial Design

MyPathway ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02091141) identifier: NCT02091141) is a multicenter, nonrandomized, open-label, multiple basket phase IIa trial ([Fig 1](#)). Eligible patients are assigned to a specific treatment cohort on the basis of the presence of a relevant target molecular alteration in their tumor biopsy.¹⁹ Patients with two or more study-eligible alterations may be treated for the

Table 1. Eligible Molecular Alterations and Testing Methods

Target Pathway	Molecular Alteration	Testing Method	Result Required for Eligibility
HER2	Overexpression or Amplification or	IHC	3+ staining
		FISH/CISH	HER2/CEP17 ratio > 2.0 or Copy number > 6
BRAF	Mutation	NGS	Copy number increased
		NGS	Activating mutation*
EGFR	Mutation	NGS	V600E mutation† or Other <i>BRAF</i> mutation
			Activating mutation‡
Hedgehog	Mutation	NGS	<i>SMO</i> activating mutation§ or <i>PTCH-1</i> loss-of-function mutation

Abbreviations: CEP17, centromeric probe for chromosome 17; IHC, immunohistochemistry; FISH/CISH, fluorescent or chromogenic in situ hybridization; HER2, human epidermal growth factor receptor-2; NGS, next-generation sequencing; *SMO*, Smoothened; *PTCH-1*, patched homolog-1.

*Includes exon 20 insertions, deletions around amino acids 755 to 759, and several nonsynonymous amino acid substitutions.

†Patients with coexisting *KRAS* mutations were excluded.

‡Includes nonsynonymous exon 18 or exon 21 mutations, or exon 19 deletions; exon 20 mutations not eligible.¹⁸

§W535L or other nonsynonymous mutations.

||Indels with ± 5 amino acids from previously described indels resulting in frameshifts; nonsense mutations ± 5 amino acids from previously reported nonsynonymous mutations.

alteration that the investigator considers most clinically relevant and may subsequently enter a different treatment cohort if they remain eligible.

Dosages of study treatments are in accordance with the United States package inserts for each product²⁰⁻²⁴ and are administered without systemic chemotherapy. Patients with HER2 molecular alterations are treated with intravenous pertuzumab (840 mg loading dose followed by 420 mg every 3 weeks) plus intravenous trastuzumab (8 mg/kg loading dose followed by 6 mg/kg every 3 weeks). Patients with *EGFR*-activating mutations are treated with erlotinib (150 mg orally once daily). Patients with *BRAF* mutations are administered vemurafenib (960 mg orally twice daily), and those with Hedgehog pathway alterations receive vismodegib (150 mg orally once daily). Patients receive treatment of two cycles (6 weeks for pertuzumab plus trastuzumab; 8 weeks for all oral agents) and are then evaluated for response. Patients with objective response or stable disease (SD) continue therapy, with repeat evaluations every two cycles for the first 24 weeks, followed by evaluations every 12 weeks, until tumor progression, unacceptable toxicity, or other discontinuation criteria are met.

Trial Oversight

The MyPathway protocol was approved by the institutional review board/ethics committee at each trial center. Written informed consent is obtained before any screening procedures. Genentech and the Sarah Cannon Research Institute designed the trial in collaboration with the MyPathway Steering Committee. The MyPathway Steering Committee meets three times per year, and when necessary, to review safety and efficacy data and preplanned futility analyses. All authors have access to the data and vouch for the accuracy and completeness of the analyses reported and for the fidelity of the trial to the protocol.

Study End Points

The primary efficacy end point for MyPathway is the objective response rate (ORR). Responses are assessed by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.¹⁷ Confirmation of response (per RECIST) is not required. Secondary efficacy end points include duration of response (DOR), progression-free survival, and 1-year overall survival. DOR is measured from the date of first documentation of an objective response to the date of tumor progression/death or

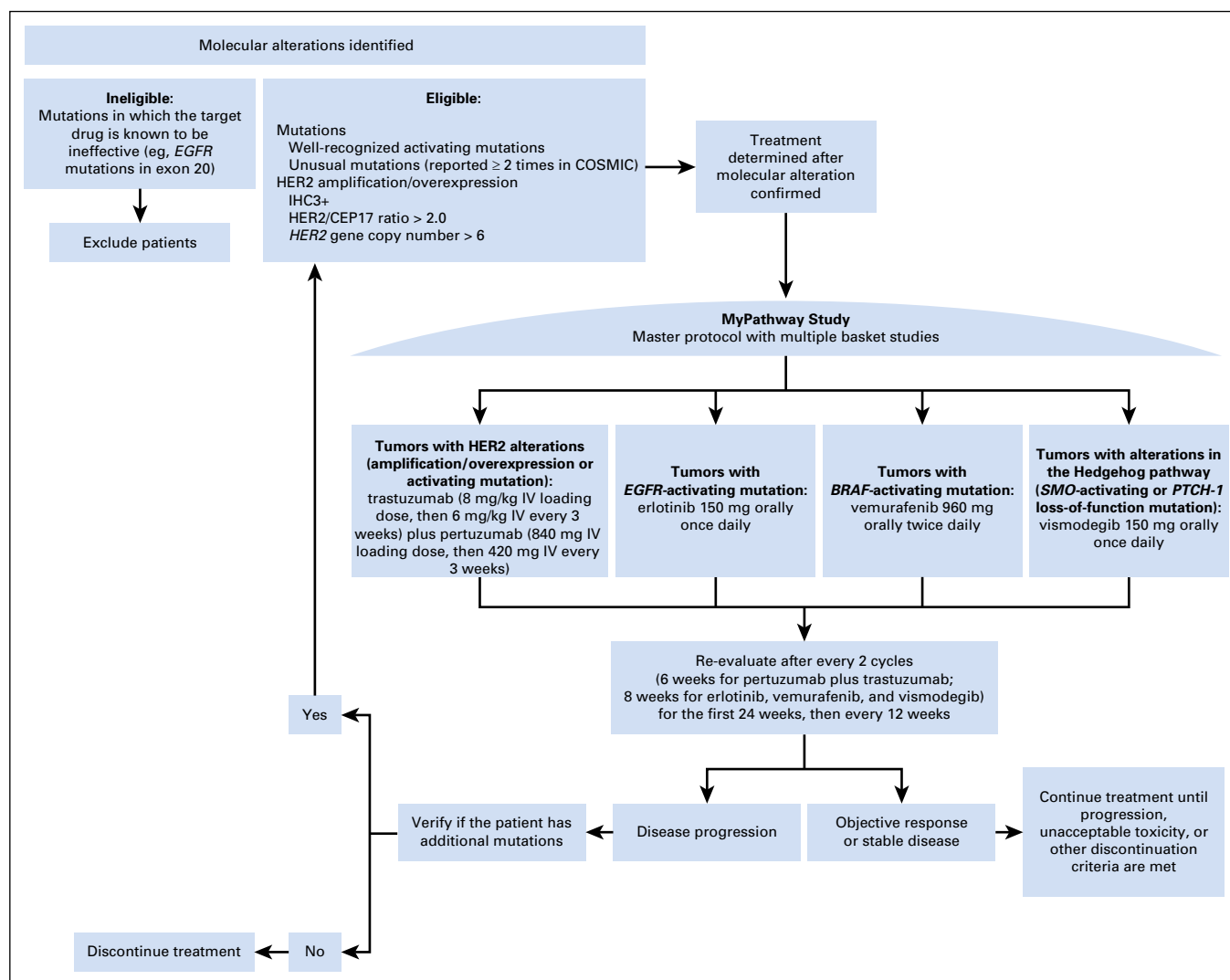


Fig 1. MyPathway study design. *BRAF*, murine sarcoma viral (v-raf) oncogene homolog B1; CEP17, centromeric probe for chromosome 17; COSMIC, Catalogue of Somatic Mutations in Cancer; *EGFR*, epidermal growth factor receptor; HER2, human epidermal growth factor receptor-2; IHC, immunohistochemistry; IV, intravenous; *PTCH-1*, patched homolog-1; q3w, every 3 weeks; *SMO*, smoothed.

the last tumor assessment (if there was no progressive disease or death). Efficacy end points are evaluated separately for each tumor-pathway cohort, as defined by specific tumor type and molecular alteration.

Statistical Analysis

Analyses of ORR were performed in the efficacy analysis population, which included patients with measurable disease who were treated and had been evaluated for tumor response or who had been discontinued from treatment for any reason before the first response evaluation. Analyses of the DOR include the efficacy analysis patients who had objective responses. The data cutoff date for this interim efficacy analysis population was November 1, 2016.

ORRs were calculated for each tumor-pathway cohort. The 95% CIs of ORR were constructed using exact binomial distribution (Clopper-Pearson estimation method). The Kaplan-Meier approach was used to estimate median DORs and their 95% CIs and median follow-up duration.

For each tumor-pathway cohort, Simon's two-stage design was used to make a preliminary assessment of treatment activity. For treatment-resistant tumor types (eg, non-small-cell lung cancer [NSCLC] and biliary), at least one response in the first 12 patients was required for cohort expansion; otherwise, the cohort was closed for futility (testing hypothesis:

ORR, 5% ν 20% at 10% one-sided type I error, 80% power). The MyPathway Steering Committee was consulted to determine treatment-resistant tumor types. For less-resistant tumor types (eg, colorectal, ovary), at least two responses in the first 13 patients were required for cohort expansion (testing hypothesis: ORR, 10% ν 25% at 10% one-sided type I error, 80% power). If preliminary activity was demonstrated, accrual to the cohort continued to a maximum of 75 patients.

The initial study protocol did not include formal plans for separate analyses of cohorts with HER2 amplification/overexpression and *HER2* mutation. However, apparent differences in tumor types and accrual of adequate numbers for analysis in each group led us to consider them separately. Similar considerations led to the separate analyses of groups with *BRAF* V600E mutations versus other *BRAF* mutations.

RESULTS

Patients

From April 1, 2014 to November 1, 2016, 251 patients with 35 different tumor types were enrolled from 38 centers in the United

States. The efficacy analysis population includes 230 patients; the remaining 21 patients had not yet reached the first efficacy evaluation. Patient demographics for the efficacy analysis group included: median age 62 years (range, 23 to 86 years), 51.0% male, 91.6% good performance status (Eastern Cooperative Oncology Group 0 or 1), and a median of 2.5 prior systemic treatment regimens (range, 0 to 9). In 107 patients, molecular alterations were detected in tumor tissue obtained at the time of diagnosis (primary site, n = 66; metastatic site, n = 37; unknown site, n = 4), whereas 123 patients had alterations detected in subsequent biopsies. Table 2 lists the tumor types and molecular alterations.

Tumor molecular alterations identified in the 230 patients were as follows: HER2, 151 (66%); BRAF, 49 (21%); Hedgehog, 21 (9%); and EGFR, nine (4%). Of the 151 patients enrolled in the HER2 arm, 114 exhibited HER2 amplification/overexpression (12 of whom also had *HER2* mutations), 36 had *HER2*-activating mutations (without amplification detected by next-generation sequencing), and one had an RBMS-NRG1 fusion (an alteration suggested to result in HER2 pathway activation). Twenty-six of the 49 patients with *BRAF*-mutated tumors had V600E mutations, whereas 23 patients had tumors with a variety of other *BRAF*-activating mutations.

Efficacy

The median duration of follow-up for the efficacy population was 9.7 months (range, 0.3 to 22.1 months). Fifty-two patients (23%) with 14 tumor types had objective responses (four complete responses [CR], 48 partial responses [PR]), and 26 additional patients had SD for > 120 days. Responses were seen with each of the four targeted treatments.

Four tumor-pathway cohorts have enrolled at least 12 patients and had protocol-mandated efficacy review: HER2 amplified/overexpressing colorectal cancer (n = 37), HER2 amplified/overexpressing NSCLC (n = 16), *HER2*-mutated NSCLC (n = 14),

and *BRAF* V600E-mutated NSCLC (n = 14). All four cohorts exceeded minimum efficacy criteria, and accrual has been extended. Several other cohorts have shown evidence of activity but have not reached the size for formal review. No tumor-pathway cohorts have been closed for lack of efficacy. However, the study was closed to further accrual of *BRAF* non-V600 mutations because of the low response rate (one of 23; 4%) in diverse tumor types.

Patients With HER2 Amplification/Overexpression

Thirty of 114 patients (26%; 95% CI, 19% to 35%) with HER2 amplification/overexpression had objective responses to treatment with trastuzumab plus pertuzumab (two CR, 28 PR). Objective responses were seen in nine primary tumor types: colorectal, bladder, biliary, salivary gland, NSCLC, pancreas, ovary, prostate, and skin (apocrine; Table 3).

Patients with HER2-amplified/overexpressing metastatic colorectal cancer composed the largest tumor-pathway cohort. In this group of 37 patients with refractory disease (median, four previous lines of therapy), treatment with trastuzumab plus pertuzumab produced PRs in 14 patients (38%; 95% CI, 23% to 55%; Fig 2A). An additional four patients had SD > 120 days. The median DOR was 11 months (range, < 1 to 16+ months; 95% CI, 2.8 months to not estimable).

Although the other tumor-pathway cohorts are relatively small, treatment with trastuzumab plus pertuzumab showed substantial activity in several other refractory tumor types. Three of nine patients (33%; 95% CI, 8% to 70%) with advanced bladder cancer had responses (one CR ongoing at 15 months; two PR lasting 1 and 6 months), and two patients had SD > 120 days (Fig 2B). Two of seven patients (29%; 95% CI, 4% to 71%) with biliary cancer had PR, and three had SD > 120 days (Fig 2C). Finally, four of five patients with salivary gland carcinoma (80%; 95% CI, 28% to > 99%) had responses (all PR).

Table 2. Tumor Types and Molecular Alterations

Primary Site	HER2	BRAF	Hedgehog Pathway	EGFR	Total
Lung, non-small-cell	30	21	3	0	54
Colorectal	40	2	0	0	42
Biliary	11*	3	0	1	15
Ovary	8	4	2	0	14
Bladder	13	0	0	0	13
Pancreas	9	4	0	0	13
Uterus	7	0	0	0	7
Breast	2†	0	2	2	6
Salivary gland	5	0	1	0	6
Small intestine	4	0	1	1	6
Prostate	1	3	1	0	5
Unknown primary	1	3	1	0	5
Other (21 tumor types)	20	9	10	5	44
Total	151 (66%)	49 (21%)	21 (9%)	9 (4%)	230

NOTE. N = 230.

Abbreviations: BRAF, murine sarcoma viral (v-raf) oncogene homolog B1; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor-2.

*One patient had a tumor with an RBMS-NRG1 fusion.

†Both had *HER2* mutations without amplification or overexpression.

Table 3. Efficacy of Treatment With Trastuzumab Plus Pertuzumab in Patients With HER2 Amplification/Overexpression

Primary Site	No. of Patients	Response, No. (%)			ORR, % (95% CI)
		CR	PR	SD > 120 Days	
Colorectal	37	0	14 (38)	4 (11)	38 (23 to 55)
Lung, non-small-cell	16	0	2 (13)	2 (13)	13 (2 to 38)
Bladder	9	1 (11)	2 (22)	2 (22)	33 (8 to 70)
Pancreas	9	0	2 (22)	1 (11)	22 (3 to 60)
Biliary	7	0	2 (29)	3 (38)	29 (4 to 71)
Ovary	8	0	1 (13)	0	13 (0 to 53)
Uterus	7	0	0	0	0
Salivary gland	5	0	4 (80)	0	80 (28 to > 99)
Other (11 sites)*	16	1 (6)	1 (6)	3 (19)	13 (2 to 38)
Total	114	2 (2)	28 (25)	16 (14)	26 (19 to 35)

NOTE. N = 114. Includes 12 patients with amplification/overexpression plus mutation.

Abbreviations: CR, complete response; ORR, objective response rate; PR, partial response; SD, stable disease.

*Responses occurred in patients with adenocarcinomas of the prostate (one) and skin (apocrine; one).

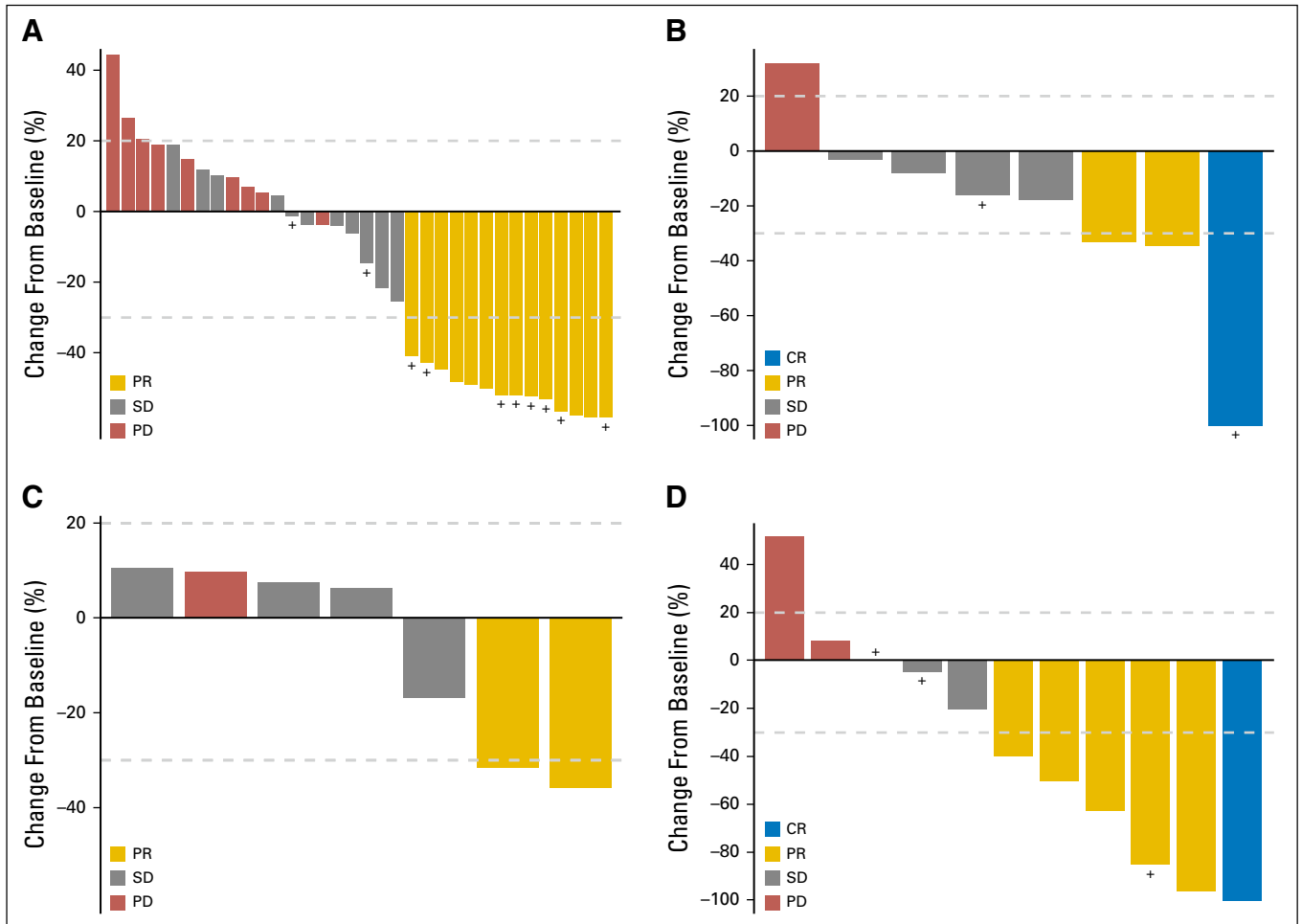


Fig 2. Waterfall plots of treatment response in patients with human epidermal growth factor receptor-2 (HER2)-amplified/overexpressing (A) colorectal, (B) bladder, and (C) biliary cancers, and (D) patients with murine sarcoma viral (v-raf) oncogene homolog B1 (*BRAF*) V600E-mutated non-small-cell lung cancer. Three patients with HER2-amplified/overexpressing colorectal cancer, one with HER2-amplified/overexpressing bladder cancer, and three with *BRAF*V600E-mutated non-small-cell lung cancer were not evaluated for response and are not included. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease. + indicates treatment is ongoing.

Patients With HER2 Mutation

Thirty-six patients received treatment with trastuzumab plus pertuzumab for tumors with *HER2* mutations (without amplification/overexpression); four of these patients (11%; 95% CI, 3% to 26%) had objective responses. Fourteen of the 36 patients with *HER2*-mutated tumors had NSCLC (adenocarcinoma, $n = 13$; adenosquamous, $n = 1$); in this group, three patients (21%; 95% CI, 5% to 51%) had PR and three had SD > 120 days. Only one of the other 22 patients with *HER2*-mutated tumors responded to treatment with pertuzumab plus trastuzumab (biliary cancer).

Patients With BRAF Mutations

Results of treatment with vemurafenib differed markedly in tumors with *BRAF* V600 mutations when compared with those with other *BRAF* mutations. Of the 26 patients with *BRAF* V600 mutations (all V600E), objective responses were seen in 12 patients (46%; 95% CI, 27% to 67%) with six different tumor types (two CR, 10 PR; Table 4). In contrast, only one of 23 patients (4%; 95% CI, 0% to 22%) with other non-V600 *BRAF* mutations had a PR (pancreas cancer with a CUX1-*BRAF* fusion). Nonresponding

BRAF mutations included: K601E ($n = 6$), G464V ($n = 2$), G469A ($n = 2$), G496A ($n = 2$), N581S ($n = 2$), and one each for G466V, G596R, G606E, L597Q, P731T, intron 9 rearrangement, intron 10 rearrangement, and MACF1- and WASFL-*BRAF* fusion.

Fourteen patients had refractory *BRAF* V600E-mutated NSCLC (adenocarcinoma, $n = 13$; sarcomatoid, $n = 1$), composing the largest tumor-pathway cohort in the *BRAF* group (Table 4). Six patients (43%; 95% CI, 18% to 71%) had objective responses (one CR, five PR), and two additional patients had SD > 120 days (Fig 2D). The median DOR was 5 months (range, 4 to 14 months).

All other tumor-pathway cohorts with *BRAF* V600E mutations were small (four or fewer patients). Assessment of treatment efficacy in these groups is therefore not yet possible.

Patients With Hedgehog Pathway or EGFR Mutations

Twenty-one patients had mutations in the Hedgehog pathway (*PTCH-1*, $n = 18$; *SMO*, $n = 3$). Three patients had PRs to vismodegib (unknown primary cancer, $n = 1$; squamous skin cancer, $n = 1$; salivary gland cancer, $n = 1$); all three patients had *PTCH-1*-mutated tumors. Various *EGFR* mutations were present in the tumors of nine

Table 4. Efficacy of Treatment With Vemurafenib in Patients With *BRAF* V600E-Mutated Cancers

Primary Site	No. of Patients	Response, No. (%)			ORR, % (95% CI)
		CR	PR	SD > 120 Days	
Lung, non-small-cell	14	1 (7)	5 (36)	2 (14)	43 (18 to 71)
Ovary	4	0	2 (50)	1 (25)	50
Colorectal	2	0	1 (50)	0	50
Unknown primary	1	0	1 (100)	0	100
Thyroid (anaplastic)	1	1 (100)	0	0	100
Head/neck (larynx)	1	0	1 (100)	0	100
Other (3 sites)	3	0	0	0	0
Total	26	2 (8)	10 (38)	3 (12)	46 (27 to 67)

NOTE. N = 26. Abbreviations: CR, complete response; ORR, objective response rate; PR, partial response; SD, stable disease.

patients who received erlotinib; one of nine patients (with urethral adenocarcinoma) achieved a PR.

DISCUSSION

MyPathway was designed to evaluate the efficacy of targeted treatments in tumors harboring activating molecular alterations in the HER2, BRAF, EGFR, or Hedgehog pathways. In 230 patients who have been treated and evaluated, all four targeted treatments have produced meaningful responses, and 14 different tumor types outside of current US Food and Drug Administration (FDA) indications have responded. Completion of accrual to MyPathway is projected to take an additional 2 to 3 years. We believe that early publication of the encouraging results in several tumor-pathway cohorts will focus attention on these groups and accelerate definitive investigation. In addition, suggestions of activity in other small cohorts may guide the design of additional studies. As a whole, these early results provide further evidence of the feasibility and potential value of the basket study design in defining the optimal use of targeted therapies.

Patients with refractory, metastatic HER2-amplified/overexpressing colorectal cancer composed the largest tumor-treatment group in this study. The incidence of HER2 amplification/overexpression is 2% to 6% in advanced colorectal cancer, accounting for approximately 2,000 patients per year in the United States.²⁵⁻²⁷ In this study, the 37 patients with colorectal cancer treated with trastuzumab plus pertuzumab had an ORR of 38% (95% CI, 23% to 55%) and a median DOR of 11 months (95% CI, 3 months to not estimable). The response rate and DOR in patients with refractory HER2-amplified/overexpressing colorectal cancer indicate that HER2 is an important driver in this malignancy and compare favorably to the response rates of other drugs recently approved for use in refractory colorectal cancer.²⁸⁻³⁰ Dual HER2-targeted therapy was also effective in the HER2 Amplification for Colorectal Cancer Enhanced Stratification (HERACLES) trial, in which eight of 27 patients with HER2-amplified/overexpressing, *KRAS* wild-type metastatic colon cancer (30%) had objective responses to treatment with trastuzumab plus lapatinib.²⁶

Results are also encouraging in other HER2-amplified/overexpressing tumor types, including bladder (33% ORR), biliary tract (29% ORR), and salivary gland (80% ORR). Although salivary duct carcinomas are rare, HER2 amplification/overexpression is common in these tumors.^{31,32} HER2 abnormalities in bladder and biliary cancers occur in 3% to 5% of patients.^{33,34} New treatment options are urgently needed in all of these treatment-refractory tumor types, and enlargement of these treatment groups is important.

Treatment with vemurafenib had notable activity in patients with refractory *BRAF* V600E-mutated cancers (46% ORR). In *BRAF* V600E-mutated NSCLC, treatment efficacy (43% ORR; median DOR, 5 months) was similar to results previously reported in two other basket trials.^{15,35} In addition to the subsets defined by EGFR, ALK, and ROS-1 alterations, patients with *BRAF* V600E-mutated NSCLC (approximately 2% of NSCLC³⁶) seem to be an important and targetable NSCLC subset. In contrast, the response rate for patients with non-V600E *BRAF* mutations was only 4%, and accrual of these patients to MyPathway has been discontinued.

The role of basket trials in identifying patient populations for targeted therapy remains unclear. To date, most basket trials have reported mixed results, which may be due to the pathways being targeted, the methods of molecular testing, or the therapeutic agents being tested. The design of MyPathway maximizes the chance of success by using CLIA-approved molecular testing readily available in the clinic and by selecting FDA-approved targeted agents backed by more than a decade of translational science and clinical experience. Although not all genetic alterations are equally actionable, the four FDA-approved targeted therapies evaluated in MyPathway produced meaningful responses in patients with various tumor types involving well-defined driver alterations.

In conclusion, current results from MyPathway demonstrate potentially clinically meaningful activity for four approved targeted regimens in multiple tumor types harboring specific molecular alterations. Durable responses were seen in patients with colorectal, bladder, biliary, and salivary duct cancers with HER2 activation/overexpression, in patients with NSCLC with *BRAF* V600E mutations, and in selected patients with *PTCH-1/SMO* or *EGFR* alterations. Treatment of additional patients in each of these groups is ongoing to better define the activity of these treatments and to further clarify the importance of molecular and histologic subgroups.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: John D. Hainsworth, Mary Beattie
Provision of study materials or patients: John D. Hainsworth, David R. Spiegel
Collection and assembly of data: Bongin Yoo
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

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Targeted Therapy for Advanced Solid Tumors on the Basis of Molecular Profiles: Results From MyPathway, an Open-Label, Phase IIa Multiple Basket Study

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