CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219249Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 130909
Request Receipt Date	3/13/2024
Product	inavolisib
Indication	PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer
Drug Class/Mechanism of Action	PI3K inhibitor
Sponsor	Genentech, Inc
ODE/Division	OND/OOD/DO1
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	5/13/2024

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes and** will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

   The proposed indication for inavolisib is in combination with palbociclib and fulvestrant for the treatment of adult patients with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment.

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 4a is checked "No," please provide the rationale in a brief paragraph below, and send the completed BTDDRT to Miranda Raggio for review so that the BTDR can be denied without MPC review. Once reviewed and cleared by

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Miranda this BTDR will be removed from the MPC calendar and you can skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

- ☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
- ☐ Undetermined
- ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐

ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐

iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐

iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐

v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history.

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[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Breast cancer is the most commonly diagnosed cancer in women, with an estimated global incidence of 2.2 million new cases annually and almost 700,000 deaths reported in 2020. Breast cancer in men is rare; accounting for less than 1% of all breast cancer cases in the United States. Locally advanced and metastatic breast cancer remains a virtually incurable disease, with the 5-year survival of patients with locally advanced or metastatic breast cancer (LA/mBC) with advanced stage at diagnosis of 31.1 months, with 29.2% of these patients likely to survive at least 5 years from the time of diagnosis. Hormone receptor (HR)-positive, HER2-negative breast cancer is the most common breast cancer subtype accounting for approximately 70% of all breast cancers. The 5-year survival of patients with HR-positive, HER2-negative LA/mBC remains low at 34% (SEER 2023).

The PI3K signaling pathway is commonly dysregulated in HR-positive breast cancer, often due to activating PIK3CA mutations. Approximately 35−40% of patients with HR-positive breast cancer have tumors that harbor mutations in PIK3CA, the gene encoding the alpha isoform catalytic subunit of the PI3K complex (i.e., p110α). PIK3CA mutations are a negative prognostic factor. Specifically, it has been estimated that patients with HR-positive, HER2-negative mBC whose tumors harbor one or more PIK3CA mutations exhibit approximately 2 months shorter progression free survival (PFS) and 8 months shorter overall survival (OS) following treatment with standard of care (SoC) as compared with patients whose tumors do not carry detectable PIK3CA mutations (Filbrunn et al 2022).

Inavolisib (RO7113755, GDC-0077) is a selective inhibitor of the PI3K catalytic subunit alpha isoform protein (p110α). In addition, inavolisib promotes the degradation of mutated p110α (mutant degrader).

Inavolisib is currently not approved in any country worldwide.

In PIK3CA-mutated breast cancer xenograft models, inavolisib reduced tumor growth, which was more pronounced in combination with palbociclib and an endocrine agent.

8. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The Sponsor has submitted results from Trial WO41554 (INAVO120). This is a phase 3 randomized, double-blind, placebo-controlled, multicenter, global trial to compare inavolisib in combination with palbociclib and fulvestrant (Inavo+Palbo+Fulv) with placebo in combination with palbociclib and fulvestrant (Pbo+Palbo+Fulv), in patients with PIK3CA-mutated, HR-positive, HER2-negative LA/mBC whose disease progressed during treatment or within 12 months of completing adjuvant endocrine therapy. This population whose disease progressed during treatment or within 12 months of completing adjuvant endocrine therapy is considered endocrine resistant. The primary endpoint of the trial is progression free survival (PFS) by investigator assessment. A sensitivity analysis for PFS by BICR was prospectively planned. Overall survival (OS) was the key secondary endpoint. Other secondary endpoints included objective response rate (ORR) based on BICR and duration of response (DoR) for responding patients, and measures of patient reported oucomes (PRO).

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease.

Clinical trial endpoints that have been used to support approval of drugs used in metastatic breast cancer include ORR, PFS, and OS.

A clinically meaningful improvement in PFS or OS has been the basis for approvals of many agents for the treatment of metastatic breast cancer.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

Patient biomarker eligibility (i.e. positive for a study-eligible PIK3CA mutation) was determined through testing of blood plasma-derived circulating tumor DNA (ctDNA) with a next-generation sequencing (NGS) assay performed at the Sponsor-designated central laboratory, or through site-directed local testing of ctDNA or tumor tissue with an polymerase chain reaction (PCR) or NGS assay.

PIK3CA mutations are considered both predictive and prognostic. Two other drugs have been approved for use in breast cancer based on PIK3CA mutation status:

- *Alpelisib is indicated in combination with fulvestrant for the treatment of adults with HR-positive, HER2-negative, PIK3CA-mutated, advanced or, metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.*

- *Capivasertib is indicated, in combination with fulvestrant for the treatment of adult patients with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.*

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population.

There are no therapies specifically approved for the first line treatment of patients with endocrine resistant LA/mBC (regardless of PIK3CA status).

The preferred first line (1L) treatment option for patients with HR-positive, HER2-negative LA/mBC includes a CDK4/6i (palbociclib, ribociclib, or abemaciclib) combined with endocrine therapy (fulvestrant or an aromatase inhibitor), in postmenopausal or pre-/peri-menopausal women (alongside an LHRH agonist) and in men. Endocrine monotherapy in the 1L setting is recommended for a small group of patients with poorer performance status and/or comorbidities, while single-agent or combination chemotherapy regimens (ie, taxanes and capecitabine) are indicated in endocrine refractory disease and/or visceral crisis.

There are additional treatment options specifically for patients with PIK3CA-mutated tumors. Alpelisib (PI3Kα inhibitor) plus fulvestrant is approved following progression on or after an endocrine-based regimen for patients with PIK3CA-mutated, HR-positive, HER2-negative LA/mBC. Recently, capivasertib (AKT inhibitor) in combination with fulvestrant has been approved for patients with HR-positive, HER2-negative LA/mBC with PIK3CA/AKT/PTEN alterations. However, neither are recommended 1L options.

Treatment options with endocrine therapy plus CDK 4/6 inhibitors, PIK3/mTOR inhibitors and chemotherapy for patients with endocrine resistant breast cancer are shown in the following tables. Of note, these therapies and patient populations are not specific to the first line therapy for HR-positive, HER2 negative LA/mBC advanced breast cancer.

Table 3 Efficacy Summary of CDK 4/6 Inhibitor-Based Regimens for the Endocrine Resistant Setting (Registrational Studies)

	Study WO41554 (INAVO120) Inavolisib + Palbociclib + Fulvestrant vs. Palbociclib + Fulvestrant	PALOMA-3[1,2,3] Palbociclib + Fulvestrant vs. Fulvestrant	MONARCH-2[4,5] Abemaciclib + Fulvestrant vs. Fulvestrant	MONALEESA-3[6,7,8,9,10] Ribociclib + Fulvestrant vs. Fulvestrant
N (ITT/patients with measurable disease)	325/325	521/406	669/482	726/560
Population	1L	1L, 2L, 3L; Pre/peri- and postmenopausal	1L, 2L: Pre/peri- and postmenopausal	1-2L (50% of ITT were endocrine sensitive), postmenopausal
***PIK3CA*-mutated (%)**	100	24.5[b]	26.5[b]	35[c]
Visceral disease (%)	78.9[b]	59.4[b]	54.9[b]	60.5[b]
Liver metastases (%)	47.8[a,b]	37[b]	26.3[b]	27.7[b]
Bone only (%)	3.1[a,b]	22[b]	27.6[b]	21.3[b]
mPFS, months (95% CI) Experimental vs Control	15.0 (11.3, 20.5) vs 7.3 (5.6,9.3) HR 0.43 (0.32, 0.59), p<0.0001	9.5 (9.2, 11.0) vs 4.6 (3.5, 5.6)[1] HR 0.461 (0.360, 0.591), p<0.0001[1]	16.4 vs. 9.3 HR 0.553 (0.449, 0.681), p<0.001	20.5 (18.5, 23.5) vs. 12.8 (10.9, 16.3) HR 0.593 (0.480, 0.732; p < 0.001)
OS (months); (95% CI)	Interim OS : NE (27.3, NE) vs. 31.1 (22.3,NE) HR 0.64 (0.43, 0.97), p=0.0338	34.9 (28.8, 40.0) vs. 28.0 (23.6,34.6) HR 0.81 (0.64, 1.03; p=0.09)[3]	46.7 vs. 37.3 (HR 0.757; 0.606, 0.945; p =0.01)	NE vs. 40.0 HR, 0.72 (0.57, 0.92; p=0.00455)[8]

	Study WO41554 (INAVO120) Inavolisib + Palbociclib + Fulvestrant vs Palbociclib + Fulvestrant	PALOMA-3[1,2,3] Palbociclib + Fulvestrant	MONARCH-2[4,5] Abemaciclib + Fulvestrant	MONALEESA-3[6,7,8,9,10] Ribociclib + Fulvestrant
ORR % (95% CI) Experimental vs Control	58.4 vs. 25%	24.6 (19.6, 30.2) vs 10.9 (6.2, 17.3)[1] for patients with measurable disease	48.1 (42.6, 53.6) vs. 21.3 (15.1, 27.6) for patients with measurable disease	40.9 (35.9, 45.8) vs. 28.7 (22.1, 35.3) for patients with measurable disease

1L-first line; 2L=second line; 3L=third line; ITT=intent-to-treat; mPFS=median progression-free survival; NE=not estimable; ORR=objective response rate; OS=overall survival.

NOTE: PFS, OS, ORR data from PALOMA-3, MONARCH-2, MONALEESA-3 are for ITT population.

Source: Inavolisib (IND 130909) Breakthrough Therapy Request Package

Table 4 Efficacy Summary of PI3K/AKT/mTOR Inhibitor-Based Regimens for Endocrine Resistant Setting (Registrational Studies)

	Study WO41554 (INAVO120) Inavolisib + Palbociclib + Fulvestrant vs Palbociclib + Fulvestrant	BOLERO-2[1,2,3] Everolimus + Exemestane vs Exemestane	SOLAR-1[a,4,5] Alpelisib + Fulvestrant vs Fulvestrant	CAPItello-291[a,6] Capivasertib + Fulvestrant vs Fulvestrant
N (ITT[a]/patients with measurable disease)	325/325	724/138	341/262	289/256
Population	1L	1L, 2L, 3L	1L 52%; 2L 47%	1L ~11%, 2L~ 64%, 3L+ ~ 25%
Endocrine resistance (%)	100	100	85	100
Prior CDK4/6i treatment (%)	1.9	0	5.3	72.9
***PIK3CA*-mutated (N)**	100	26	100	76
Visceral disease (%)	78.9[c]	56[c]	55.0[c]	66.5[c]
Liver metastases (%)[b]	47.8[b,c]	33[c]	29.0[c]	45.2[c]
Bone only (%)[b]	3.1[b,c]	NR	24.9[c]	16.1[c]
mPFS, months (95% CI) Experimental vs Control	15.0 (11.3, 20.5) vs 7.3 (5.6, 9.3) HR 0.43 (0.32, 0.59), p<0.0001	7.8 vs 3.2[1] HR 0.45 (0.38, 0.54), p<0.0001[1]	11.0 (7.5, 14.5) vs.- 5.7 (3.7,7.4) HR 0.65 (0.50, 0.85), p < 0.001	7.3 (5.5, 9.0) vs. 3.1 (2, 3.7) HR 0.50 (0.38, 0.65)
OS (months); (95% CI)	Interim OS: NE (27.3, NE) vs 31.1 (22.3, NE) HR 0.64 (0.43, 0.97), p=0.0338	31.0 (28.0, 34.6) vs 26.6 (22.6, 33.1) HR 0.89 (0.73, 1.10; p = 0.14)[2]	Final OS: 39.3 vs 31.4 months HR 0.86 (0.64, 1.15); p = 0.15[5]	Interim OS HR 0.69 (0.45–1.05)
ORR % Experimental vs Control	58.4 vs 25%	12.6 vs 1.7%[3]	26.6 vs 12.8%	29 vs 10%[7]
DOR (months)	18.4 vs 9.6	NR	NR	9.4 vs 8.6

Source: Inavolisib (IND 130909) Breakthrough Therapy Request Package

Table 5 Efficacy Summary for Chemotherapy Options in the First-Line Treatment Setting for HR-positive, HER2-negative LA/mBC

	Capecitabine [1]	Weekly Paclitaxel [2]	Docetaxel + Capecitabine [3]	Paclitaxel + Gemcitabine [4]
N (ITT/patients with measurable disease)	484/—	275/—	255/255	266/266
Visceral disease (%)	See [1]	78[2]	See [3]	72.9[4]
Liver metastases (%)	See [1]	—	45[3]	—
Bone only (%)	—	—	—	—
mPFS (months)	6.0–7.9[1]	6.6[2] For HR+: 12.4[2]	6.1 (5.4-6.5)[3]	5.9 vs 3.9[4]
mOS (months)	18.6–29.4[1]	26.6[2]	14.5 (12.3-16.3)[3]	18.6 vs 15.8[4]
ORR (%) (measurable disease unless otherwise specified)	21–26.1[1]	38.0[2]	42 (36-48)[3]	All: 41.4 vs 26.2[4] Visceral: 35.6 vs 21.9[4]
DOR (months) (in pts with measurable disease unless otherwise specified)	—	—	7.3 (6.9-8.4)[3]	9.89 vs 8.44[4]

DOR=duration of response; ITT=intent-to-treat; mPFS=median progression-free survival; ORR=objective response rate; mOS=median overall survival.

Source: Inavolisib (IND 130909) Breakthrough Therapy Request Package

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

There are no other drugs for a similar indication for PIK3CA-mutated breast cancer that have requested breakthrough therapy designation.

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

11. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

Results from Trial WO41554 (INAVO120), a phase 3 randomized, double-blind, placebo-controlled, multicenter, global study to compare inavolisib in combination with palbociclib and fulvestrant (Inavo+Palbo+Fulv) with placebo in combination with palbociclib and fulvestrant (Pbo+Palbo+Fulv), in patients with PIK3CA-mutated, HR-positive, HER2-negative LA/mBC whose disease progressed during treatment or within 12 months of completing adjuvant endocrine therapy were submitted to support this BTDR. A total of 325 patients were randomized in a 1:1 ratio with 161 patients and 164 patients randomized to the Inavo+Palbo+ Fulv arm and Pbo+Palbo+ Fulv arm, respectively.

The primary endpoint of the study was PFS by investigator assessment. A sensitivity analysis for PFS by BICR was prospectively included. Overall survival (OS) was the key secondary endpoint. Other secondary endpoints included objective response rate (ORR) based on BICR and duration of response (DoR) for responding patients, and measures of patient reported oucomes (PRO).

Trial WO41554 met its primary endpoint at the time of the clinical cutoff date, when a total of 195 PFS events had occurred. The addition of inavolisib to the combination of palbociclib and fulvestrant demonstrated a statistically significant improvement in investigator-assessed PFS in patients with PIK3CA-mutated, HR-positive, HER2-negative LA/mBC (stratified HR = 0.43 [95% CI: 0.32, 0.59], p < 0.0001). The median PFS was 15.0 months (95% CI: 11.3, 20.5) versus 7.3 months (95% CI: 5.6, 9.3), in the Inavo+Palbo+ Fulv arm vs Pbo+Palbo+ Fulv arm respectively . These results were supported by the BICR-assessed median PFS, which was 16.4 months in the Inavo+Palbo+ Fulv arm vs. 7.4 months in the Pbo+Palbo+ Fulv arm (stratified HR=0.50; 95% CI: 0.36, 0.68; log-rank p-value< 0.0001).

At the planned interim analysis for the key secondary endpoint of OS, a total of 97 events had occurred (63% of planned OS events). The stratified HR was 0.64 (95% CI: 0.43, 0.97; p = 0.0338), with 42 deaths in the Inavo+Palbo+ Fulv arm and 55 deaths in the Pbo+Palbo+Fulv arm. Under the interim analysis stopping boundary (p≤ 0.0098), statistical significance was not reached.

ORR was numerically higher in the Inavo+Palbo+Fulv arm compared to Pbo+Palbo+Fulv , (58.4% [95% CI: 50.4, 66.1] vs. 25.0% [95% CI: 18.6, 32.3]) respectively. Median DOR in responders was 18.4 months [95% CI: 10.4, 22.2] in the Inavo+Palbo+Fulv arm () and 9.6 months [95% CI: 7.4, 16.6] in the Pbo+Palbo+Fulv arm .

The data provided from Trial WO41554 demonstrates a statistically significant and clinically meaningful improvement in investigator assessed PFS for patients treated with invavolisib. These results were supported by BICR assessed PFS results. The OS results at the time of the interim analysis did not reach statistical significance but the results were in favor of treatment with inavolisib. First line treatment with Inavo+Palbo+Fulv in patients with endocrine resistant, PIK3CA-mutated, HR-positive, HER2-negative advanced breast cancer appears better than other available therapies.

b. Include any additional relevant information.

The safety profile of inavolisib in combination with palbociclib and fulvestrant were consistent with the known safety profiles of the individual study treatments (palbociclib, fulvestrant and other PI3K inhibitors).

The majority of patients in both treatment arms (98.8% Inavo+Palbo+Fulv vs. 100.0% Pbo+Palbo+Fulv) reported at least one AE with the most frequent AEs of any grade being neutropenia (54.3% vs. 54.9%), hyperglycemia (53.7% vs. 7.4%), and diarrhea (48.1% vs. 16.0%). Adverse events which occurred at a higher frequency (≥10% of patients in either arm with a difference of ≥5% between treatment arms) in the Inavo+Palbo+Fulv arm compared with the Pbo+Palbo+Fulv arm were hyperglycemia, diarrhea, stomatitis, nausea, fatigue, decreased appetite, COVID-19,

[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

headache, mucosal inflammation, alopecia, weight decreased, hypokalemia, vomiting, urinary tract infection, and dry skin.

The incidence of Grade 3-4 AEs and highest grade was comparable between the Inavo+Palbo+Fulv (85.8%) and Pbo+Palbo+Fulv (82.1%) arms of which the incidence rates were driven by Grade 3-4 AEs of neutropenia (88.9% vs. 90.7%)(. The majority of Grade 3-4 AEs in both treatment arms were associated with myelosuppression.

Grade 5 AEs were reported in 6 patients (3.7%) in the Inavo+Palbo+Fulv arm and 2 patients (1.2%) in the Pbo+Palbo+Fulv arm. Grade 5 AEs reported in the Inavo+Palbo+Fulv arm were cerebral hemorrhage, cerebrovascular accident, gastrointestinal hemorrhage, acute coronary syndrome, death and COVID-19. Grade 5 AEs reported in the Pbo+Palbo+Fulv arm were COVID-19 pneumonia and cardiac arrest.

Adverse event of special interest (AESI) are based on the known and evolving safety profile of inavolisib. AESIs include hyperglycemia, diarrhea, rash, stomatitis/mucosal inflammation,and neutropenia.

12. Division's recommendation and rationale (pre-MPC review:

☒ GRANT:

Provide brief summary of rationale for granting.

The data provided from Trial WO41554 demonstrates a statistically significant and clinically meaningful improvement in investigator assessed PFS for patients treated with invavolisib. These results were supported by BICR assessed PFS results. The OS results at the time of the interim analysis did not reach statistical significance but the results were in favor of treatment with inavolisib. First line treatment with Inavo+Palbo+Fulv in patients with endocrine resistant, PIK3CA-mutated, HR-positive, HER2-negative advanced breast cancer appears better than other available therapies.

☐ DENY:

Provide brief summary of rationale for denial: N/A

13. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The sponsor submitted an original NDA on March 27, 2024. The sponsor is also submitting a PMA to CDRH for a companion diagnostic for selection of PIK3CA-mutated breast cancer.

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation: N/A

14. List references, if any:

National Cancer Institute. Surveillance, Epidemiology and End Result Program (SEER) Explorer Application. Available from https://seer.cancer.gov/explorer/application.php (updated 2023).

Fillbrunn M, Signorovitch J, André F et al. PIK3CA mutation status, progression and survival in advanced HR + /HER2- breast cancer: a meta-analysis of published clinical trials. BMC Cancer. 2022;22(1):1002-13.

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 2-26-2024 /M. Raggio

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUPARNA B WEDAM
05/07/2024 10:36:30 AM

PREETI NARAYAN
05/07/2024 11:35:32 AM

LALEH AMIRI KORDESTANI
05/07/2024 12:23:13 PM

IND 130909

MEETING MINUTES

Genentech, Inc.
Attention: Robin Stewertson
Regulatory Program Management
1 DNA Way, MS 407B
South San Francisco, CA 94080

Dear Robin Stewertson:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for inavolisib.

We also refer to the teleconference between representatives of your firm and the FDA on January 26, 2024. The purpose of the meeting was to discuss and obtain agreement from the Agency on the acceptability of the proposed clinical data package to form the basis of an NDA for inavolisib in patients with PIK3CA-mutated, HR-positive, HER2-negative locally advanced or metastatic breast cancer.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, contact Ja'Kaya Wilson, Regulatory Project Manager, at Jakaya.wilson@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ja'Kaya Wilson, MS
Regulatory Project Manager
Oncology 1 Group
Division of Regulatory Operations for Oncologic Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

{See appended electronic signature page}

Preeti Narayan, MD
Acting Clinical Team Lead
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	February 5, 2024
Meeting Location:	Via ZOOM
Application Number:	IND 130909
Product Name:	Inavolisib
Indication:	Breast cancer
Sponsor Name:	Genentech, Inc.
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair:	Preeti Narayan, MD
Meeting Recorder:	Ja'Kaya Wilson

FDA ATTENDEES

Laleh Amiri-Kordestani, MD	Division Director, DO1
Preeti Narayan, MD	Clinical Team Leader, DO1
Suparna Wedam, MD	Clinical Reviewer, DO1
Hong Zhao, PhD	Clinical Pharmacology Team Lead, DCPII
Hairat Sabit, PhD	Clinical Pharmacology Reviewer, DCPII
Tiffany Ricks, PhD	Supervisory Pharmacologist Reviewer, DHOT
Yang Nan, PhD	Drug Product Quality Reviewer, OPQ
Xing Wang, PHD	Senior Pharmaceutical Quality Assessor, OPQ
Haley Gittleman, PhD	Biostatistics Reviewer, DBV
Joyce Cheng, PhD	Biostatistics Team Leader, DBV
Timothy Schaefer, PhD	Scientific Reviewer, CDRH
Tien Truong, PhD	Genomics Reviewer, DOTPM
Jeffrey Kraft, PhD	Genomics Team Leader, DTPM
Christy Cottrell	Chief, Project Management Staff, DRO-OD
Ja'Kaya Wilson, MS	Regulatory Project Manager, DRO-OD

SPONSOR ATTENDEES

Sravanthi Cheeti, MS-Pharm	Sr. Principal Scientist, Clinical Pharmacology Lead
Jacob Devine, MA	Principal Scientist, Patient Centered Outcomes
Parker Downing, PharmD	Regulatory Program Manager
Weize Huang, PharmD, PhD	Principal Scientist, Clinical Pharmacology
Yanling Jin, MSc	Sr. Statistical Scientist

Sam Lim	Associate Safety Director, Safety Science
Tong Lu	Clinical Pharmacology Modeling and Simulation
Colin Neate, MSc	People and Product Leader, Data & Statistical
Christiane Rothkegel, PhD	Sr. Regulatory Program Director, Global
Noopur Shankar, MD	Medical Safety Director, Safety Science Lead
Guicheng (Gracie) Sheng, MS	Technical Regulatory Program Director
Chunyan Song, MD	Group Medical Director, Global Development Lead
Robin Stewertson	Regulatory Program Director, US Regulatory Lead
Thomas Stout, PhD	Principal Clinical Scientist
Eirini Thanopoulou, MD	Lead Clinical Director, Clinical Science Filing Lead

1.0 BACKGROUND

Genentech requested a Type B pre-NDA meeting with FDA to seek feedback on the acceptability of a regulatory submission that will support approval of inavolisib. Genentech plans to submit a New Drug Application (NDA) for inavolisib in March 2024 based primarily on data from Study WO41554 and supported by data from the phase 1 Study GO39374.

Inavolisib is an inhibitor of the PI3K catalytic subunit alpha isoform protein (p110α) and promotes the degradation of mutated p110α. The proposed indication is:

Study WO41554 is a phase 3, randomized, double-blind, placebo controlled, multicenter, trial designed to compare the efficacy, safety, and tolerability of the combination of inavolisib+palbociclib+fulvestrant (Inavo+Palbo+Fulv) vs. placebo+palbociclib+fulvestrant (Pbo+Palbo+Fulv) in patients with PIK3CA-mutated, HR-positive, HER2-negative LA/mBC whose disease progressed during treatment or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease. The primary endpoint was progression free survival (PFS) by investigator assessment. Key secondary endpoints included overall survival (OS), overall response rate (ORR), duration of response (DOR), clinical benefit rate (CBR) and patient reported outcomes.

Patients were stratified by visceral disease (yes or no), endocrine resistance (primary or secondary) and geographic region (North America/Western Europe, Asia, other). Patient biomarker eligibility determined through testing of blood plasma derived circulating tumor DNA (ctDNA) with a next-generation sequencing (NGS) assay performed at the Sponsor-designated central laboratory, or through site-directed local testing of ctDNA or tumor tissue with a polymerase chain reaction (PCR) or NGS assay.

Regardless of whether the central test or local test was used for biomarker-eligibility determination, all participants were required to submit both blood and tissue samples for central assessment.

A total of 325 patients were randomized on study: 161 patients in the inavolisib arm and 164 patients in the placebo arm. One patient randomized to the inavolisib arm did not receive treatment. At the data cut off of September 29, 2023, a total of 208 patients had discontinued from all study treatment (93 patients in the inavolisib arm and 115 patients in the placebo arm) with the most common reason being progressive disease. The median duration of follow-up for all patients was 21.3 months (inavolisib: 21.3 months; placebo: 21.5 months)

Patients were recruited from 123 centers across 28 countries, including 120 patients, 125 patients and 80 patients from Asia, North America/Western Europe and "Other" (Russia, Turkey, Ukraine, Australia, Argentina, Georgia, Brazil, and New Zealand) regions, respectively. There were only 16 patients enrolled in the United States. The majority of patients had not received prior adjuvant CDK4/6i therapy (321 patients) but had received prior (neo)-adjuvant chemotherapy (269 patients) or prior (neo)- adjuvant endocrine therapy (323 patients).

Study WO41554 met its primary endpoint of PFS assessed by investigator. The median PFS was 15.0 months (95% CI: 11.3, 20.5) for the inavolisib treatment arm vs. 7.3 months (95% CI: 5.6, 9.3) for the placebo arm with a stratified HR=0.43 ([95% CI: 0.32, 0.59], p<0.0001). Sensitivity analysis on PFS by Blinded Independent Central Review (BICR), supported the primary endpoint results (stratified HR = 0.50 [95%CI: 0.36, 0.68], p < 0.0001, median PFS: 16.4 months [95% CI: 11.1, 22.0] vs. 7.4 months [95% CI: 5.8, 9.2]). OS was the key secondary endpoint evaluated under Type I error control per the hierarchical testing procedure pre-specified in the SAP. At the interim analysis, the OS results (stratified HR = 0.64; [95% CI: 0.43, 0.97], p < 0.0338) were immature (information fraction 63% and median follow-up 21.3 months) and did not cross the statistical significance boundary (p = 0.0098). The objective response rate (ORR) by investigator was 58.4% (95% CI: 50.4, 66.1) in the inavolisib treatment arm compared to 25% (95% CI: 18.6, 32.3).

The AEs (by preferred terms) of any grade reported in ≥30% of patients were:

- Inavo+Palbo+Fulv arm: neutropenia, hyperglycemia, diarrhea, neutrophil count decreased, anemia, stomatitis

- Pbo+Palbo+Fulv arm: neutropenia, neutrophil count decreased, anemia

AEs reported with a higher frequency (≥5%) in the Inavo+Palbo+Fulv arm compared to the Pbo+Palbo+Fulv arm included hyperglycemia, diarrhea, stomatitis, nausea, decreased appetite, fatigue, COVID-19, and headache. Grade 3-4 AEs occurred in 88% of patients in the Inavo+Palbo+Fulv treatment arm and 82% in the Pbo+Palbo+Fulv

treatment arm. The proportion of patients experiencing serious adverse events (SAEs) was higher in the Inavo+Palbo+Fulv arm compared to the Pbo+Palbo+Fulv arm (24.1% patients vs. 10.5% patients). The SAEs were distributed across multiple PTs and no PTs occurred with a ≥2% difference between the Inavo+Palbo+Fulv and Pbo+Palbo+Fulv arms. The SAEs occurring in ≥2 patients in the Inavo+Palbo+Fulv arm were: COVID-19, pneumonia, urinary tract infection, diarrhea, anemia, febrile neutropenia, pyrexia, acute coronary syndrome. Discontinuation of inavolisib or placebo treatment due to AEs occurred in 6% patients in the Inavo+Palbo+Fulv arm and 1% patients in Pbo+Palbo+Fulv.

Hyperglycemia is a reversible on-target toxicity associated with PI3K inhibitors and was reported in 95 patients in the inavolisib treatment arm and in 14 patients in the placebo arm. Among the inavolisib treated patients who had hyperglycemia, the median time to the first onset was 7 days. One patient discontinued inavolisib due to hyperglycemia. There were no serious hyperglycemia events reported. The majority of events in the inavolisib treatment arm were Grade 1 (26 patients) or Grade 2 (60 patients); Grade 3 events occurred in 9 patients and there were no Grade 4 events. Of the patients that received treatment for hyperglycemia (66 patients) in the inavolisib treatment arm, 62 patients and 8 patients received treatment with metformin or insulin, respectively. Among patients with at least one hyperglycemia event reported, hyperglycemia events had resolved in the 75/95 patients in the inavolisib treatment arm and 13/14 patients in the placebo arm. Dose interruptions or reductions of inavolisib for management of hyperglycemia occurred in 44 patients (27.2%) and 4 patients (2.5%), respectively.

Study GO39374 is a phase 1, open-label, dose-escalation study evaluating the safety, tolerability, and pharmacokinetics of inavolisib as a single agent in patients with locally advanced or metastatic PIK3CA-mutated solid tumors and in combination with endocrine and targeted therapies in patients with locally advanced or metastatic PIK3CA-mutated breast cancer. There were no eligibility restrictions with respect to patients' endocrine sensitivity or resistance.

Per study arm-specific inclusion criteria, study participants were assigned to one of seven regimens:

- inavolisib as a single agent (Stage I; Arm A)
- inavolisib in combination with palbociclib and letrozole (Stages I and II; Arm B)
- inavolisib in combination with letrozole (Stages I and II; Arm C)
- inavolisib in combination with fulvestrant (Stage II; Arm D)
- inavolisib in combination with palbociclib and fulvestrant (Stage II; Arm E)

- inavolisib in combination with palbociclib and fulvestrant and metformin (Stage II; Arm F)

- inavolisib in combination with trastuzumab and pertuzumab (Stage II; Arm G).

A total of 191 patients were enrolled across Arms A-F, including 33 patients enrolled in Arm B, 20 patients enrolled in Arm E and 21 patients enrolled in Arm F.

In Arm B, the objective response rate (ORR) as assessed by the investigator was 52% with a median duration of response (DOR) of 42.3 months (95% CI: 14.7, NE). In Arm E, the ORR as assessed by the investigator was 40% with a median DOR of 11.9 months (95% CI: 7.6, 33.4). In Arm F, the ORR as assessed by the investigator was 16.7% with a median DOR of 9.2 months (95% CI: 9.1, NE).

The most frequently reported AEs (≥50%) by preferred term were neutropenia, diarrhea, anemia, hyperglycemia, thrombocytopenia, and nausea in Arm B; hyperglycemia, diarrhea, nausea, vomiting, mucosal inflammation, and neutropenia in Arm E; hyperglycemia, diarrhea, nausea, and neutropenia in Arm F.

2.0 DISCUSSION

Question 1: *Does the Agency agree that the efficacy and safety results from the pivotal Phase III WO41554 (INAVO120) study and the supporting Phase I Study GO39374 provide sufficient evidence to support approval of the use of inavolisib in the proposed indication:*

FDA Response to Question 1: **Whether the results from INAVIO120 and Study GO39374 will be sufficient to support an approval for the use of inavolisib for the proposed indication will be a review issue. We have the following general comments at this time and may request additional information during the review:**

a. **INAVO120 only enrolled patients with endocrine resistant BC. In the NDA submission provide adequate data to support your proposed broad indication.**

b. **We note more patients received prior tamoxifen than an AI in the adjuvant setting and subgroup analysis show differential efficacy. Include rationale in the submission for applicability of this trial's results to a US population.**

c. **Clarify how data from GO39374 is considered supportive of the proposed NDA submission.**

d. **We note the overall response from arm F of study GO39374 shows a lower response rate than arm E, clarify any reasons for this difference.**

Refer also to Additional Comments.

Sponsor's Response to Question 1:

Response 1a. The Sponsor acknowledges that the INAVO120 study only enrolled patients with first-line, endocrine resistant, advanced breast cancer (ABC). The (b) (4) collective preclinical and clinical evidence that a triple blockade with inavolisib in combination with palbociclib and fulvestrant, can prevent, overcome, and/or delay treatment resistance and lead to favorable benefit/risk in patients with *PIK3CA* mutated, HR+, HER2- ABC, regardless of the endocrine resistant or sensitive setting.

In detail:

- There is strong scientific rationale, confirmed by robust preclinical data (in vitro and in vivo), that simultaneous blockade of the three key oncogenic signaling pathways in HR+, HER2-, *PIK3CA*-mutated ABC, namely ER, PI3K/mTOR, and CDK4/6 pathways, results in synergistic and prolonged tumor suppression and regression compared to any other monotherapy or doublet combination strategy. Hence, such triplet blockade treatment strategy is predicted to have the potential to prevent, overcome, or delay treatment resistance, which is translated to better clinical outcomes (Vora et al. 2014; Herrera-Abreu et al. 2016; Cortés et al. 2017; O'Brien et al. 2020; Song et al. 2022). These preclinical data were observed in both endocrine sensitive and resistant models. Specifically, a triplet combination could overcome treatment resistance to PI3K inhibitor-based therapy (Vora et al. 2014; O'Brien et al. 2020), or resistance to CDK4/6 inhibitor-based therapy (Herrera-Abreu et al. 2016; O'Brien et al. 2020), or prevent the onset of treatment resistance in endocrine sensitive models (O'Brien et al. 2020; Song et al. 2022). Past attempts of investigating similar triplet combinations in Phase I/II trials were abandoned because of challenging safety and tolerability (Tolaney et al. 2021; Pascual et al. 2021). The unique dual mechanism of action of inavolisib resulted in an improved therapeutic window and combinability, which enabled a triplet combination that was evaluated in INAVO120.

- INAVO120 is the first Phase III, randomized trial that tested a triplet combination of a PI3Kα inhibitor (inavolisib), a CDK4/6 inhibitor (palbociclib) and endocrine therapy (fulvestrant), and demonstrated a statistically significant and clinically meaningful PFS benefit (stratified HR = 0.43 [95% CI: 0.32, 0.59]) with an improvement in mPFS from 7.3 to 15 months, which was supported by BICR-PFS and was consistently observed in key subgroups and secondary efficacy endpoints; a clear positive trend of OS benefit (stratified HR: 0.64 [95% CI: 0.43, 0.97]) and clinically meaningful improvements in other secondary endpoints including ORR, DOR, and CBR. The substantially favorable benefit/risk of the

inavolisib triplet combination demonstrated in INAVO120 provides definitive clinical validation of the scientific rationale and preclinical data on the synergy of the triple blockade of PI3K, CDK4/6, and ER signaling in *PIK3CA*-mutated, HR+, HER2- ABC.

- The data from the Phase I GO39374 study showed consistently promising anti-tumor activity (efficacy) of the inavolisib triplet combinations, in terms of ORR, DOR, CBR, and PFS, regardless of endocrine backbone (letrozole or fulvestrant) or treatment setting, ranging from endocrine sensitive to heavily pretreated endocrine resistant settings, across multiple treatment lines. The Sponsor considers this is indicative of the clinical benefit that the inavolisib triplet blockade can bring to all patients with *PIK3CA*-mutated, HR+, HER2- ABC.

- Long-term safety data from the Phase I GO39374 study, in 193 patients (overall safety population), demonstrated that 61 patients (31.6%) were treated with an inavolisib-based combination for 1 year or longer (up to ~ 4 years) comprising the long-term safety cohort. The safety and tolerability profile of the long-term safety cohort was consistent with the overall safety population, and there was no evidence of new or unexpected safety signals. Overall, the acceptable long-term safety and tolerability of the inavolisib-based combinations support the applicability of the triplet combination in settings where longer duration of treatment is expected, like the endocrine sensitive setting (Bedard PL et al. 2022).

  In conclusion, the Sponsor considers that the unique dual mode of action of inavolisib led to a wide therapeutic index and enabled a tolerable and efficacious triplet combination with a CDK4/6i and an endocrine agent and realized the synergy of the triplet pathway blockade to more effectively prevent or delay treatment resistance in *PIK3CA*-mutated, HR-positive, HER2-negative BC regardless of therapy setting. The substantial magnitude of clinical benefit and the manageable safety, tolerability and maintenance of QoL from Study WO41554, and the supportive safety and efficacy data from Study GO39374 (arms B, E, and F), demonstrate a compelling benefit-risk profile. In light of the mechanism of action, paired with the totality of the available preclinical and clinical data, the Sponsor considers that the *PIK3CA* mutation biomarker selected ABC patient population may benefit from the inavolisib triplet combination, regardless of endocrine sensitivity or resistance to prior treatments and at any treatment setting. (b) (4)

<u>Meeting Discussion for 1a:</u> The FDA acknowledged the Sponsor's response. The proposed broad indication will be a review issue. Detailed rationale that a triplet regimen is required for all patients in the proposed indication should be included in the submission along with data.

Response 1b. The Sponsor acknowledges the comment and would like to provide clarifications on the subgroup data of patients treated with prior adjuvant tamoxifen in INAVO120 and how it may impact the applicability to the US population.

Proportion of Patients treated with prior adjuvant tamoxifen:

The NCCN guidelines recommendations for adjuvant ET for premenopausal women with early BC (eBC) include: tamoxifen (TAM) with or without ovarian suppression or ovarian suppression plus an aromatase inhibitor (AI). The NCCN recommendations for postmenopausal patients include: 1. an AI; 2. TAM followed by switching to an AI; 3. TAM for up to 10 years. The NCCN guidelines recommendations for adjuvant ET in patients with eBC are consistent with other international guidelines (Loibl S et al. 2023; Park YH et al. 2020).

INAVO120 was designed to include only first-line, endocrine resistant, HR+, HER2-, *PIK3CA*-mutated ABC patients. This led to an enrichment of a patient population with poor prognostic clinicopathological characteristics, which are more often seen in younger patients. The median age of 54 in INAVO120 reflected this younger patient population and led to a higher proportion of patients, who were pre-/peri-menopausal (38.2% of the ITT population), compared to other clinical trials in HR+, HER2- ABC, like PALOMA-3 (21% of the ITT population; Turner N et al. NEJM 2015). This aspect may explain the higher proportion of patients that received adjuvant tamoxifen in line with the NCCN guidelines.

Subgroup Analyses by prior adjuvant ET:

Exploratory analyses of investigator-assessed PFS were performed to investigate the consistency of primary endpoint findings across a number of pre-specified subgroups defined by baseline prognostic factors, including prior ET. In line with this, the study was not powered for statistical testing in these subgroups and so these analyses are intended to only provide descriptive information for the primary endpoint. Therefore, while numerical difference in the observed hazard ratio and 95% CI estimates for prior Tamoxifen (HR: 0.38, 95% CI: 0.25,0.59) and prior AI (HR: 0.62, 95% CI: 0.41,0.94) is acknowledged, this exploratory subgroup analysis is considered to be consistent with the overall PFS analysis and supportive of the benefit of the addition of inavolisib to palbociclib and fulvestrant, regardless of the type of prior adjuvant ET. Additionally, the subgroup analysis of PFS for pre-/peri-menopausal (HR: 0.35, 95% CI: 0.22,0.56) and post-menopausal (HR:0.64, 95% CI: 0.44,0.92) patients are also consistent in supporting the clinically meaning treatment benefit demonstrated for the primary endpoint.

Overall Conclusion: Taken together, the observed higher proportion of patients that received adjuvant tamoxifen can be explained by the higher proportion of younger, pre-/peri-menopausal patients, the majority of whom are treated with adjuvant tamoxifen-based therapy. The Sponsor considers that the subgroup analysis demonstrates consistent benefit in patients with prior tamoxifen and prior AI, supporting the primary endpoint and that the INAVO120 results are applicable to the US patient population, as a tamoxifen-based and an AI-based regimens are recommended by NCCN guidelines

in the adjuvant setting and are widely implemented in US clinical practice.

Meeting Discussion for 1b: No discussion.

Response 1c. The Sponsor acknowledges the Agency's comment and wishes to clarify that the safety and efficacy data from Study GO39374 will provide supportive data in addition to INAVO120 to ensure adequate characterization of efficacy, safety, and tolerability of inavolisib in combination with palbociclib and an endocrine therapy in patients with *PIK3CA*-mutated HR+, HER2- ABC.

Data from Study GO39374 will support the dose selection for the INAVO120 trial. Study GO39374 was the first-in-human study for inavolisib-based combinations, and as such included a dose escalation phase, which provided the data and justification for the dose selection (9mg QD) for inavolisib.

Moreover, data from Study GO39374 will enhance the safety database for inavolisib based combinations (aggregate data from Arms A-F), including additional data for patients, who were enrolled with higher baseline Fasting Blood Glucose (FBG $\leq$ 140 mg/dL) and HbA_{1C} levels (HbA_{1C} <7%) compared to the eligibility criteria for the INAVO120 trial. This will further support the applicability of the inavolisib triplet combination in patients with underlying risk factors for hyperglycemia.

Furthermore, the promising anti-tumor activity (efficacy) data, in terms of ORR, DOR, CBR, and PFS from Study GO39374 will support the applicability of the inavolisib triplet combination with different endocrine agents, namely letrozole (Arm B: 33 patients) and fulvestrant (Arms E and F: 40 patients); the applicability of the triplet in different treatment settings, ranging from endocrine sensitive to heavily pretreated endocrine resistance (Arms B, E, and F), acknowledging the caveats of non-randomised clinical data and relatively small sample size.
Taken together, the promising clinical activity and manageable safety and tolerability data from Study GO39374 in a broad population, across multiple lines of therapy, in the endocrine resistant and sensitive setting, along with the compelling scientific rationale of the synergy of the simultaneous triplet blockade, is to complement the substantial benefit/risk profile demonstrated by the inavolisib triplet combination in INAVO120, in support of the proposed broad indication statement in patients with *PIK3CA*-mutated, HR-positive, HER2-negative ABC.

Meeting Discussion for 1c: The FDA acknowledged the Sponsor's response. Ultimately, whether the limited data from Study GO39374 can support the proposed broad indication will be a review issue.

Response 1d. The Sponsor acknowledges the Agency's comment and wishes to clarify that patients enrolled in Arm F were more heavily pre-treated compared to Arm E. Specifically, 62% pts in Arm F were treated with more than two lines of prior therapy in the metastatic setting, whereas 60% of patients in Arm E received up to 2 prior lines of therapy in the metastatic setting. Moreover, 62% of patients in Arm F received prior

chemotherapy vs 20% in Arm E, 66.7% received prior CDK4/6 inhibitors compared to 0%, and 66.7% received prior fulvestrant compared to 15%, respectively. The number and type of prior therapies is a recognised factor that can impact the ORR of a treatment regimen. This is in line with clinical trials with targeted therapies, like alpelisib (SOLAR-1; Andre F et al, 2019 vs BYLieve trial; Rugo H et al, 2021) and capivasertib (CAPI-tello 291; Turner N et al, 2023).

Although one of the objective of Arm F was to assess the role of metformin in patients at higher risk of developing hyperglycemia ($HbA_{1C} \geq 5.7\%-<7\%$ and BMI ≥ 30 kg/m^2), the median cumulative inavolisib dose intensity in Arm F was comparable to Arm E (89.1% vs. 90.5%). There was not a significant difference in the incidence of all grade AEs nor grade 3-4 AEs. There were also similar discontinuation rates due to AEs for inavolisib in both arms (10%), indicating that the observed differences in the ORR is unlikely to be attributable to differences in safety and tolerability between the two arms.

In summary, the observed lower overall response rate from Arm F of Study GO39374 compared with Arm E can be attributed to the fact that Arm F patients were significantly more pretreated compared to Arm E patients. The Sponsor plans to also provide this data in the NDA dossier.

Meeting Discussion for 1d: No discussion.

Question 2: *Does the Agency agree that the requirement for a dedicated DDI study can be waived due to the low likelihood of DDI between inavolisib and CYP3A4 substrates?*

FDA Response to Question 2: **No. We strongly recommend you continue your ongoing dedicated clinical DDI study between inavolisib and CYP3A substrates. Currently, there is low confidence in predicting simultaneous inhibition and induction mechanisms using PBPK modeling and in vitro data. In your planned NDA submission, submit your in vitro data, including assessment of the endogenous CYP3A biomarkers, and a complete PBPK modeling report and modeling files. The determination of the DDI risk between inavolisib and CYP3A substrates will be based on the totality of evidence.**

Sponsor Response: The Sponsor thanks the Agency and acknowledges the comments. Due to enrollment and feasibility challenges despite mitigation measures, recruitment of patients into the clinical DDI study (GP43040) of inavolisib as a single agent with a sensitive CYP3A4 substrate, midazolam, has unfortunately been terminated. The Sponsor confirms that a complete PBPK modeling report and modeling files, in vitro DDI assessment, and clinical endogenous biomarker assessment will be included in the NDA submission. No discussion required.

Meeting Discussion: No discussion.

Question 3: *In support of the NDA based on the positive clinical results from Study*

WO41554, does the Agency agree with the proposal to include 9 months primary drug product stability data and up to 36 months supportive stability data at the time of the NDA submission?

FDA Response to Question 3: **Your proposal to submit 9 months' stability data for the drug product primary batches along with up to 36 months supportive stability data at the time of initial NDA submission may be acceptable. Any additional data submitted 30 days after the initial submission may or may not be reviewed depending on internal review timelines and available resources. The expiration dating period for the proposed drug product will be determined at the time of NDA review based on available data consistent with the recommendations of ICH Q1E.**

Sponsor Response: The Sponsor thanks the Agency and acknowledges the comment. No discussion required.

Meeting Discussion: No discussion.

ADDITIONAL COMMENTS:

1. **Include in the NDA submission an overview of diversity in the trial by race, ethnicity, and age. Provide rationale for any underrepresented racial or ethnic groups. We noted for instance, that enrollment of Black and African American patients is not representative of the US population with HR+/HER2-negative breast cancer.**

Sponsor Response: The Sponsor acknowledges the Agency's comment. An overview of diversity in WO41554 by race, ethnicity, and age will be provided in the NDA dossier, as well as the rationale for any observed underrepresentation of the US population with HR+, HER2- breast cancer.

Regarding Proposed Dosage for the Planned Phase 3 Trial:

2. **You have not provided adequate justification with supporting data for your selected dosage of inavolisib 9 mg QD in combination with palbociclib + fulvestrant. Based on the data you provided, very limited number of patients were treated at inavolisib dose levels other than 9 mg QD. The difference in responses across the dose range studied appeared minimal while there was a dose-dependent increase in adverse events. It is not known if the 9 mg QD dosage for inavolisib is an optimized dosage in Study INAVO120. In your planned NDA submission, provide adequate justifications with supporting data for your dose selection.**

Sponsor Response: The Sponsor acknowledges the Agency's comment and confirms

that the dose justification based on supporting data will be provided in the NDA to support the 9 mg QD dose selection.

Regarding Your Planned Submission:

Sponsor Response to Comments 3. through 10. The Sponsor thanks the Agency and acknowledges comments 3. through 10.

3. **The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application should be consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" (available https://www.fda.gov/media/74346/download). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.**

4. **Address the following questions in the Summary of Clinical Pharmacology:**

   a. **What is the basis for selecting the doses and dosing regimen used in the trials intended to support your marketing application? Identify individuals who required dose modifications and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.**

   b. **What are the exposure-response relationships for efficacy, safety and biomarkers?**

   c. **How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?**

5. **Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.**

6. **Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with minimum and maximum values as appropriate.**

7. **Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.**

   - **Provide all concentration-time and derived pharmacokinetic parameter**

datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

- **Identify individual subjects with dose modifications; the time to the first dose reduction, interruption, or discontinuation; the reasons for dose modifications in the datasets.**

8. **Submit the following for the population pharmacokinetic analysis reports:**

   - **Standard model diagnostic plots Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line.**
   - **Model parameter names and units in tables.**
   - **Summary of the report describing the clinical application of modeling results.**
   - **Refer to the following pharmacometrics data and models submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.**

9. **Submit the following information and data to support the population pharmacokinetic analysis:**

   - **SAS transport files (*.xpt) for all datasets used for model development and validation.**
   - **A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.**
   - **Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)**

10. **Submit a study report describing exploratory exposure-response (measure of effectiveness, biomarkers, and safety) relationships in the targeted patient population. Refer to Guidance for Industry for population PK, exposure-response relationships, and pharmacometrics data and models submission guidelines.**
11. **Use the laboratory analysis dataset (adlb.xpt) for the laboratory-based**

adverse reactions and the adverse event analysis dataset (adae.xpt) for the non-laboratory-based adverse reactions (individual and pooled terms as appropriate) to evaluate the exposure-response relationship for safety and the effect of intrinsic and extrinsic factors on safety based on the maximum toxicity grade compared to baseline.

Sponsor Response: The Sponsor acknowledges the Agency's comment. For assessing exposure-response relationships for laboratory-based adverse events, such as neutropenia, anemia, and thrombocytopenia, laboratory analysis dataset (adlb.xpt) will be used and for non-laboratory based adverse events, such as diarrhea, stomatitis, and hyperglycemia, adverse event analysis dataset (adae.xpt) will be used. No discussion required.

12. **Include a variable that identifies the maximum toxicity grade compared to baseline for laboratory-based adverse reactions in laboratory analysis dataset (adlb.xpt) and for non-laboratory-based adverse reactions (individual or pooled where applicable) in adverse event analysis dataset (adae.xpt) to support these analyses. A description of the pooled non-laboratory-based adverse reactions should be provided in the reviewer guide and consistent with common pooled terms used to inform labeling if applicable.**

Sponsor Response: The Sponsor acknowledges the Agency's request and agrees to provide the variable and definitions for pooled terms from non-laboratory-based adverse events in our data package. Variables can be found in the data package along with data specifications. The variable for maximum grade for both baseline and post baseline for laboratory parameters will be included in the data package as well. No discussion required.

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Discussion: **No discussion needed**

3.0 IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our December 18, 2023 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VII. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[2]

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would

[2] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[3]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of

[3] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology

the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating, "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[4]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[5] and Pregnancy and Lactation Labeling Final Rule[6] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

[4] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[5] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[6] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidance's.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidance's.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information, please visit FDA.gov.[7]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[8]

[7] http://www.fda.gov/ectd
[8] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[9]

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims.*

SUBMISSIONS WITH REAL-WORLD EVIDENCE

CDER strongly encourages sponsors to include information in their submission cover letters that identifies uses or proposed uses of real-world evidence (RWE) to support a regulatory decision regarding product safety and/or effectiveness. For recommendations on specific information to include in submission cover letters, see the guidance for industry *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products.*[10] For questions or clarification, contact cdermedicalpolicy-realworldevidence@fda.hhs.gov.

[9] https://www.fda.gov/media/85061/download
[10] https://www.fda.gov/media/124795/download

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JAKAYA N WILSON
02/13/2024 10:33:57 AM

PREETI NARAYAN
02/13/2024 10:39:31 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 130909

MEETING MINUTES

Genentech, Inc.
Attention: Alex Morris, PharmD, RPh
1 DNA Way
South San Francisco, CA 94080

Dear Dr. Morris,

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GDC-0077.

We also refer to the meeting between representatives of your firm and the FDA on July 11, 2019. The purpose of the meeting was to discuss the nonclinical and clinical development plans, and the proposed Phase 3 study and registrational strategy for GDC-0077, in combination with palbociclib and fulvestrant, for the treatment of patients with locally advanced or metastatic phosphatidylinositol 3-kinase (PIK3CA) mutant, hormone receptor (HR)-positive, HER2 negative breast cancer with disease progression on or after prior adjuvant endocrine therapy.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call LT Mitchell Chan, Regulatory Project Manager at (301) 796-9105.

Sincerely,

{See appended electronic signature page}

Mitchell Chan, PharmD, BCPS
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation & Research

Sincerely,

{See appended electronic signature page}

Harpreet Singh, MD
Clinical Team Leader (Acting)
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation & Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES
These Meeting Minutes Supersede Minutes From July 19, 2019

Meeting Type:	B
Meeting Category:	Pre-Phase 3
Meeting Date and Time:	July 11, 2019; 3:00 PM – 4:00 PM EST
Meeting Location:	WO22/Rm1309
Application Number:	130909
Product Name:	GDC-0077
Indication:	(b) (4) [redacted]
sponsor/Applicant Name:	Genentech, Inc
Meeting Chair:	Julia Beaver, MD
Meeting Recorder:	LT Mitchell Chan

FDA ATTENDEES
Julia Beaver, MD, Director, DOP1
Laleh Amiri-Kordestani, MD, Supervisory Associate Director, DOP1
Danielle Krol, MD, Clinical Reviewer, DOP1
Preeti Narayan, MD, Clinical Reviewer, DOP1
Sakar Wahby, PharmD, Clinical Reviewer, DOP1
Harpreet Singh, MD, Clinical Reviewer, DOP1
Tiffany Ricks, PhD, Pharmacologist/Toxicologist Team Leader, DHOT
Erik Bloomquist, PhD, Supervisory Mathematical Statistician, DBV
Diqiong Xie, PhD, Mathematical Statistician, DBV
Pengfei Song, PhD, Clinical Pharmacology Team Leader, DCPV
Wentao Fu, PhD, Clinical Pharmacology Reviewer, DCPV
Soma Gosh, PhD, Supervisory Reviewer, CDRH
Karen Bijwaard, MS, RAC, MB (ASCP), CQA, Scientific Master Reviewer, CDRH
LT Mitchell Chan, PharmD, BCPS, Regulatory Project Manager, DOP1

SPONSOR ATTENDEES
Jennifer Schutzman, MD, PhD, Lead Medical Director
Jennifer Lauchle, MD, Lead Group Medical Director
Leah Kristin Schutt, DVM, DVSc, DACVP, DABT, Nonclinical Program Lead
Key Kang, Group Leader, Regulatory

Anjali Vaze, MD, Senior Medical Director, Safety Science
Luna Musib, PhD, Associate Director, Clinical Pharmacology
Michael Joseph Mamounas, Director, Project Team Leader
Alex Morris, PharmD, RPh, Associate Program Director, Regulatory
Peter Trask, PhD, MPH, Associate Director, Patient Center Outcomes Research
Leslie Dickmann, PhD, MPH, Senior Scientist, Clinical Pharmacology
Katherine Emily Huthinson Feigerle, PhD, Scientist, Oncology Biomarker Development
Tiffany Hung, PhD, Project Leader, Companion Diagnostics
Carlos E Jara-Garate, PharmD, Post-Doctoral Fellow, Regulatory
Elina Asikanius, Principal Statistical Scientist
Xiaobo Bai, PhD, Senior Regulatory Affairs Specialist, Foundation Medicine, Inc.

1.0 BACKGROUND

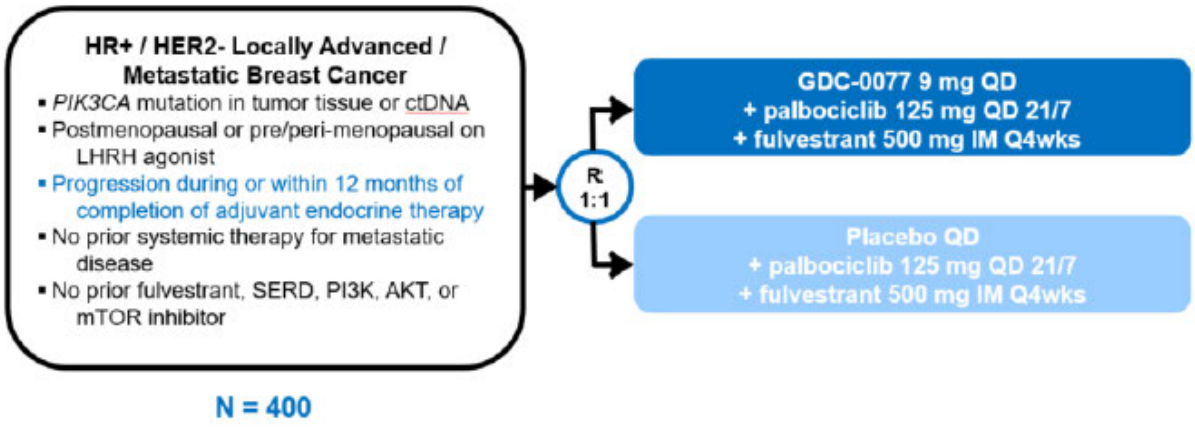
The sponsor proposes a Phase 3, randomized, double-blind, placebo-controlled trial to compare the efficacy and safety of the triplet combination of GDC-0077, palbociclib and fulvestrant versus placebo plus palbociclib and fulvestrant in post-menopausal or LHRH treated pre/peri-menopausal female patients with locally advanced or metastatic, *PIK3CA*-mutant, HR+/HER2− breast cancer with disease progression during treatment or within 12 months of completion of adjuvant endocrine therapy.

GDC-0077 is a PI3Kα inhibitor which is currently being evaluated as a monotherapy and in combination with palbociclib, fulvestrant, letrozole, and metformin in multiple arms of a Phase 1/1b study of 115 patients as of February 2019 the MTD was found to be 9 mg daily. The most frequent adverse events are hyperglycemia (grade ≥3 16.5%) and diarrhea. In Arm B, patients (n=32) were treated with GDC-007 in combination with palbociclib and letrozole. The most common AEs were neutropenia, diarrhea, hyperglycemia and thrombocytopenia. Arm E evaluated GDC-0077 in combination with palbociclib and fulvestrant in 3 patients, and Arm F evaluated the same triplet combination but with the addition of metformin in 4 patients that had a BMI >30 kg/m^2 or had an HgbA1c >5.7%. The AEs experienced in both arms were decreased appetite, diarrhea, nausea, stomatitis, and hyperglycemia.

The planned registrational study WO41554 will enroll 400 patients at approximately 175 investigative sites globally. The study will include post-menopausal and LHRH-treated pre/peri-menopausal women with PIK3CA mutations in tumor tissue or ctDNA. Patients must have had progressive disease during or within 12 months of completion of adjuvant endocrine therapy and no prior systemic therapy for metastatic disease. Patients will be randomized to GDC-0077 + palbociclib + fulvestrant vs oral placebo + palbociclib + fulvestrant. Patients will be stratified by visceral disease, endocrine resistance, and region.

Of note, the sponsor plans to exclude patients with Type 1 and Type 2 diabetes mellitus and restrict enrollment for patients at high risk of diabetes based on a fasting glucose <126 and HbA1C <5.7%. In the interim the sponsor is enrolling patients with known risk factors for hyperglycemia (BMI ≥30 kg/m^2 and HgA1c ≥5.7%) onto Arm F of their Phase 1/1b study, in which patients are treated with the triplet regimen + metformin.

Proposed Study Design:



Stratification factors

1. Visceral disease
2. Endocrine resistance (primary vs. secondary)
3. Region

Primary Endpoint	Investigator-assessed PFS
Secondary Endpoints	• Safety and PRO • ORR, DoR • OS

The primary endpoint will be investigator-assessed PFS. Secondary endpoints will include overall survival (OS), objective response rate (ORR), duration of response (DOR), best overall response rate (BOR), clinical benefit rate (CBR), time to deterioration (TTD) in pain, and TTD in physical function (PF), role function (RF), and global health survey (GHS)/health related quality of life (HRQoL).

The study has a 90% power to detect a HR of 0.65, corresponding to an improvement in median PFS from 11 to 16.9 months. The minimal detectable difference for the PFS HR is 0.77 (i.e., an improvement of 11 to 14.3 months in median PFS).

2. DISCUSSION

Question 1: Does the agency agree that the proposed nonclinical toxicology program is sufficient to support the registration of GDC-0077 in combination with palbociclib and fulvestrant for the proposed indication?

FDA Response to Question 1: Your proposed nonclinical toxicology program appears appropriate to support a marketing application of GDC-0077 for the proposed indication. The adequacy of the data to support approval will be determined following review of your NDA submission.

Company Response: The sponsor acknowledges and thanks the agency for the feedback and has no further comments. No further discussion is required.

Question 2: Does the agency agree that the proposed clinical pharmacology program is sufficient to support registration of GDC-0077 in combination with palbociclib and fulvestrant in the proposed indication?

FDA Response to Question 2: Your proposed clinical pharmacology program appears sufficient in terms of food effect evaluation, population PK analysis and exposure-response analysis.

We have the following recommendations regarding GDC-0077 drug-drug interaction (DDI) potential:

1. **We agree that a dedicated DDI study to investigate GDC-0077 in combination with palbociclib and fulvestrant is not needed. Continue clinical DDI potential evaluation with PK data collected in your proposed Phase 3 Study WO41554.**

2. **You should conduct a dedicated DDI study to evaluate the DDI potential of GDC-007 on the PK of a sensitive CYP3A4 substrate.**

3. **You should conduct dedicated DDI studies to evaluate the DDI potential of a strong CYP3A4 inhibitor or inducer on GDC-0077 PK unless you can provide data to justify CDC-0077 is not a CYP3A4 substrate.**

See Additional Comments regarding QTc prolongation evaluation.

Company Response: The sponsor acknowledges and thanks the agency for the feedback and will take these recommendations under advisement. Please see company response under additional comments regarding QTc prolongation evaluation.

Question 3: Does the agency agree that the target patient population of the Phase III Study WO41554 is adequately defined per the study eligibility criteria to support the following proposed indication?

FDA Response to Question 3: Yes, your target population is acceptable.

If you choose to modify your inclusion criteria to enroll patients with diabetes, you will need to inform us as well as provide the rationale based on your ongoing Phase 1 study (Arm F GDC-0077 in combination with palbociclib and fulvestrant + metformin).

We recommend that men and women are eligible for enrollment. Provide a scientific rationale if you propose to exclude men from your trial.

Company Response: The sponsor acknowledges and thanks the agency for the feedback regarding the eligibility criteria for the planned Phase III study. In the future, if the sponsor intends to modify the eligibility criteria for the planned Phase III study to enroll patients with diabetes, the sponsor will plan to inform the agency and provide rationale based on data from the GDC-0077 Phase I/Ib study and/or available public data from other PI3K-alpha or PI3K pathway inhibitors that inform best practices for safe administration in patients with diabetes. Regarding the agency's recommendation that men and women are eligible for enrollment, the sponsor will modify eligibility requirements accordingly to allow enrollment of male patients with breast cancer. In addition, the agency noted that the sponsor also plans to restrict enrollment for patients at high risk of diabetes based on a fasting glucose <126 and HbA1C <5.7%. During the conduct of the planned Phase III study, the sponsor intends to modify the eligibility criteria based on emerging data across the GDC-0077 Phase I/Ib study, including Arm F, from the current requirement for HbA1c <5.7% to more broadly include pre-diabetic patients with HbA1c <6.5%. This broader inclusion of pre-diabetic patients may include enhanced glucose monitoring and management plans.

Discussion: The sponsor's plan to inform the agency should they choose to broaden their eligibility criteria to enroll diabetic and pre-diabetic patients is acceptable. The agency noted that patients may have received CDK4/6 inhibitors in the adjuvant setting. This along with all prior therapies will need to be documented.

Question 4: Does the agency agree with the selection of the combination partners (GDC-0077+palbociclib+fulvestrant) and comparators (placebo + palbociclib + fulvestrant) for the proposed target patient population of the Phase III study?

FDA Response to Question 4: Yes; however, provide a rationale as to why you would not include a treatment arm of GDC-0077 and fulvestrant (Arm D of your Phase 1/1 b trial).

In your informed consent, you will need to include language which states that patients are foregoing treatment with alpelisib.

Company Response: The sponsor acknowledges and thanks the agency for the feedback regarding the selection of the combination partners and comparators for the planned Phase III study.

The current standard-of-care first-line treatment for patients with HR+/HER2- metastatic breast cancer, with disease progression on or after prior adjuvant endocrine therapy, is endocrine therapy in combination with a CDK4/6 inhibitor. Available data indicate that patients whose cancer harbors PIK3CA mutation derive a similar relative PFS benefit compared with patients whose cancer does not harbor PIK3CA mutation when a CDK4/6 inhibitor is combined with endocrine therapy (Cristofanilli et al. Lancet Onc 2016). These data support that the current standard-of-care first-line treatment with a CDK4/6 inhibitor and endocrine therapy is appropriate for patients whose tumors harbor PIK3CA mutation. In nonclinical studies, the addition of GDC-0077 to palbociclib results in greater tumor growth inhibition and regressions compared with either single agent in PIK3CA-mutant xenografts (Edgar et al. AACR 2017). Further, nonclinical data demonstrate that addition of a PI3K-alpha inhibitor prevented resistance

to CDK4/6 inhibitor treatment in a patient-derived xenograft model (Herrera-Abreu et al. Cancer Res 2016). Thus, the planned Phase III study is aimed at evaluating whether upfront dual blockade of PI3K and CDK4/6 signaling may achieve greater anti-tumor activity and delay or prevent resistance to the standard-of-care combination of palbociclib + fulvestrant.

Given the established standard-of-care use of a CDK4/6 inhibitor and endocrine therapy as first-line treatment, the sponsor believes a PI3K-alpha inhibitor and fulvestrant combination is important to evaluate for safety and efficacy in patients who have already received a CDK4/6 inhibitor. Although the full spectrum of resistance mechanisms to CDK4/6 inhibitor and endocrine therapy combinations remains to be elucidated, acquired PIK3CA mutations have been reported and present an opportunity for therapeutic intervention (O'Leary et al. Cancer Disc 2018). The sponsor is evaluating the safety and anti-tumor activity of the GDC-0077 and fulvestrant combination in the ongoing Phase I/Ib study (Arm D) in patients who have received prior CDK4/6 inhibitor therapy to inform further development of this combination and how it may integrate into standard-of-care treatment patterns that include first-line treatment with a CDK4/6 inhibitor.

The sponsor agrees that a thorough discussion of the risks/benefits of available standard therapies should occur during the informed consent process. However, the range of treatment options and risk/benefit considerations for any given treatment may be specific to an individual patient and, for example, may include or extend beyond treatment with alpelisib. Patients with HR+/HER2- advanced or metastatic breast cancer have a number of treatment options, including endocrine therapy alone or combined with one of three approved CDK4/6 inhibitors or with a PI3K pathway inhibitor, including alpelisib or everolimus. In addition, CDK4/6 inhibitor and endocrine therapy combinations remains the established standard of-care first-line treatment for HR+/HER2- metastatic breast cancer regardless of tumor PIK3CA mutation status and patients will receive this combination in both arms of the planned Phase III study, with or without the addition of PI3K-alpha inhibition with GDC-0077.

The sponsor proposes to include the following language in the Informed Consent Form to ensure an appropriately thorough discussion of the risks/benefits of available standard therapies occurs between the treating investigator and the patient prior to consent to participate in the study:

<u>Discussion:</u> We acknowledge your rationale for selection of combination partners and comparator for the proposed study. This is acceptable.

<u>Question 5:</u> Does the agency agree that the proposed dose and schedule of GDC-0077 in combination with palbociclib and fulvestrant in the Phase III Study WO41554 is appropriate to

assess the safety and efficacy of GDC-0077, when administered in the proposed combination, in the target patient population?

FDA Response to Question 5: No. You have only provided safety data for 3 patients who have been treated with your proposed regimen of GDC-0077 in combination with palbociclib and fulvestrant.

Given the limited clinical experience of GDC-0077 in the proposed combination, we recommend that you further evaluate the safety and efficacy of the proposed GDC-0077 dosing regimen in the combination using emerging data from Study GO039374 before initiating the proposed Phase 3 trial. Pool clinical pharmacokinetic, pharmacodynamic, activity and safety data, as well as nonclinical pharmacology data, to conduct integrated dose-response and exposure-response analyses for dose optimization.

Company Response: The sponsor acknowledges and thanks the agency for the feedback.
It is the sponsor's position that safety for GDC-0077 in combination with palbociclib and fulvestrant is informed by the totality of safety data across Arms of the Phase I/Ib study. The GDC-0077 safety profile is expected for PI3K-alpha inhibition and similar safety has been observed when GDC-0077 is administered as a single agent and in combination with letrozole or fulvestrant. Based on review of the available data for palbociclib in combination with either letrozole or fulvestrant, the sponsor does not believe safety or tolerability differs based on the different endocrine therapy partner. Based on comparable safety when palbociclib is combined with letrozole or fulvestrant, and similarly comparable safety when GDC-0077 is combined with letrozole or fulvestrant, the sponsor does not anticipate differences in the safety profile of the triplet combination of GDC-0077 + palbociclib + fulvestrant compared with the triplet combination of GDC-0077 + palbociclib + letrozole where more data is available.
In GDC-0077 combinations with palbociclib (n=50 patients with letrozole or fulvestrant as of 04 July 2019), no new safety events have been observed, although stomatitis, reported with other PI3K and CDK4/6 inhibitors (Andre et al. NEJM 2019; Mayer et al. Clin Cancer Res 2019; Turner et al. NEJM 2015; Finn et al. NEJM 2016), is more frequent than GDC-0077 combinations with endocrine therapies, and remains predominantly Grade 1-2.
Based on the agency's feedback, we have provided updated available safety information as of 04 July 2019 from a total of 17 patients who have been enrolled and received treatment with 9 mg daily GDC-0077 + palbociclib + fulvestrant in Arms E (7 patients) and F (10 patients, + metformin) of the ongoing Phase I/Ib Study GO39374 as summarized below.
The emerging safety data from these 17 patients is consistent with the observed safety with GDC-0077 in combination with palbociclib and letrozole, with no new safety signals. The current mean time on study is 74 days (1-198 days) and thus limits an assessment of efficacy at this time.

The following summary of safety data is from a snapshot of study data on 04 July 2019 (clinical cutoff date 03 July 2019). No specific data cleaning processes were undertaken.
In Arm E (n= 7, GDC-0077 + palbociclib + fulvestrant), AEs regardless of relationship occurring in 2 or more patients include diarrhea (5 patients), nausea (4 patients), hyperglycemia, mucosal inflammation, neutropenia, and stomatitis (3 patients each), and decreased appetite, dyspnea, epistaxis, fatigue, oropharyngeal pain, rash, vomiting, and weight decreased (2 patients each).

Seven Grade ≥ 3 AEs, regardless of relationship, were reported in four patients including neutropenia (2 patients) and hyperglycemia, dysphagia, nausea, mucosal inflammation, and paraesthesia (1 patient each). Neutropenia, hyperglycemia, mucosal inflammation, and paraesthesia were attributed to study treatment (GDC-0077 and/or palbociclib and/or fulvestrant), however, dysphagia and nausea were assessed as unrelated to study treatment and attributed to the patient's underlying malignancy by the investigators.
Two SAEs occurred in 1 patient and included Grade 3 dysphagia and Grade 2 vomiting. Neither SAE was attributed to study treatment by the investigator and instead considered related to the underlying malignancy.

In Arm F (n=10 GDC-0077 + palbociclib + fulvestrant + metformin), AEs regardless of relationship occurring in 3 or more patients include nausea (7 patients), diarrhea and hyperglycemia (5 patients each), stomatitis (4 patients), and oropharyngeal pain (3 patients).
Nine Grade ≥ 3 AEs, regardless of relationship, were reported in four patients including hyperglycemia (3 patients), neutropenia and fatigue (1 patient, includes 2 events of fatigue), and electrocardiogram ST segment depression, cellulitis, and osteomyelitis (1 patient each). Hyperglycemia, neutropenia, and fatigue were attributed to study treatment (GDC-0077 and/or palbociclib and/or fulvestrant and/or metformin), while electrocardiogram ST segment depression, cellulitis, and osteomyelitis were assessed as unrelated to study treatment by the investigators.

Four SAEs occurred in 2 patients and included Grade 2 pulmonary hemorrhage and Grade 3 electrocardiogram ST segment depression in one patient, and Grade 3 events of cellulitis and osteomyelitis in one patient. None of these SAEs were attributed to study treatment by the investigators.

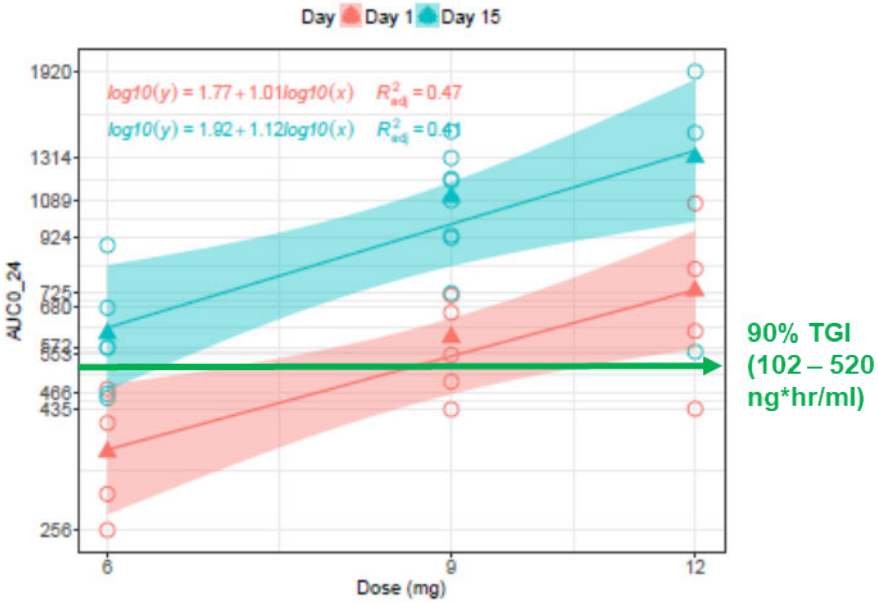
No deaths have been reported in Arms E and F. Three patients have discontinued study treatment; 2 patients discontinued study treatment due to progressive disease and 1 patient withdrew consent.

The sponsor anticipates Arms E and F will be fully enrolled (n=20 patients each) within the next 4-6 months and is closely monitoring the emerging safety, efficacy, and PK data.
In summary, expanded experience with the GDC-0077, palbociclib, and fulvestrant combination has not identified new safety concerns and supports that triplet combination safety does not differ based on the endocrine therapy partner. Thus, the sponsor believes the overall safety data for GDC-0077 combinations with palbociclib support the selection of 9 mg daily GDC-0077 in combination with palbociclib and fulvestrant for the planned Phase III study.

Dose-response and Exposure-response analysis

A. Rationale for GDC-0077 dose based on exposure and preclinical efficacy models
The sponsor compared GDC-0077 exposures in patients to the relevant exposures in mice where efficacy was achieved in tumor xenograft models. Single agent GDC-0077 AUC associated with 90% tumor growth inhibition (TGI) in mouse PIK3CA-mutant xenograft models (HCC-1954 and KPL4 breast cancer cell lines) was also compared to observed AUC from the GDC-0077 single-agent arm of Study GO39374. As shown in the figure below, the exposure associated with 9 mg

daily GDC-0077 at steady-state in all patients was consistently above the exposure associated with 90% TGI while some patients (2/6 or 33.3%) did not achieved this exposure at 6 mg daily.



B. Rationale for GDC-0077 dose based on tumor growth inhibition modeling analysis using data from Study GO39374

The sponsor performed Tumor Growth Inhibition (TGI) modeling using the pooled data from Study GO39374 to infer the effect of GDC-0077 on suppressing tumor growth. This model-based approach is based on previous work on a Modeling & Simulation (M&S) framework developed for oncology (Claret L., et al., 2009; Bruno R., et al., 2014; Claret L., et al., 2018), and the sponsor believes this approach provides support for dose selection based on efficacy for the proposed Phase III study.

The analysis was conducted with data from 97 patients with 423 tumor size assessments (represented by the sum of longest diameters [SLD]) collected in the Study GO39374 across study arms as of the clinical cut-off date of 29 Mar 2019. Figure 1 shows the observed longitudinal tumor size vs. time-profile for each patient. Based on their shared impact on estrogen receptor signaling, letrozole and fulvestrant combination arms were grouped. Thus, the following treatment groups were analyzed: (1) GDC-0077 single agent (Arm A), (2) GDC-0077 + fulvestrant or letrozole (Arms C and D), and (3) GDC-0077 + palbociclib + fulvestrant or letrozole (Arms B, E and F).

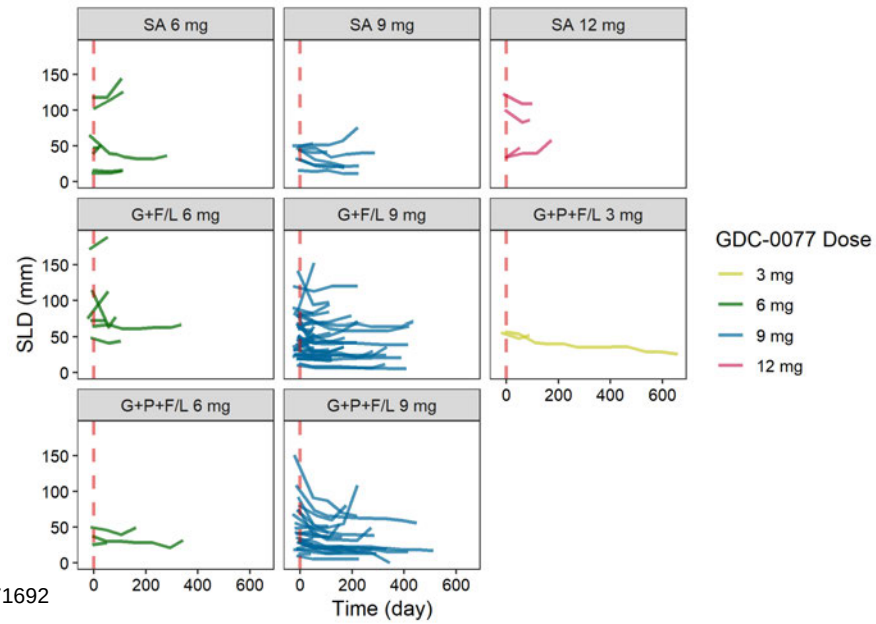


Figure 1: Observed Individual Tumor-size (sum of longest

diameters) vs. Time-profile in Study GO39374

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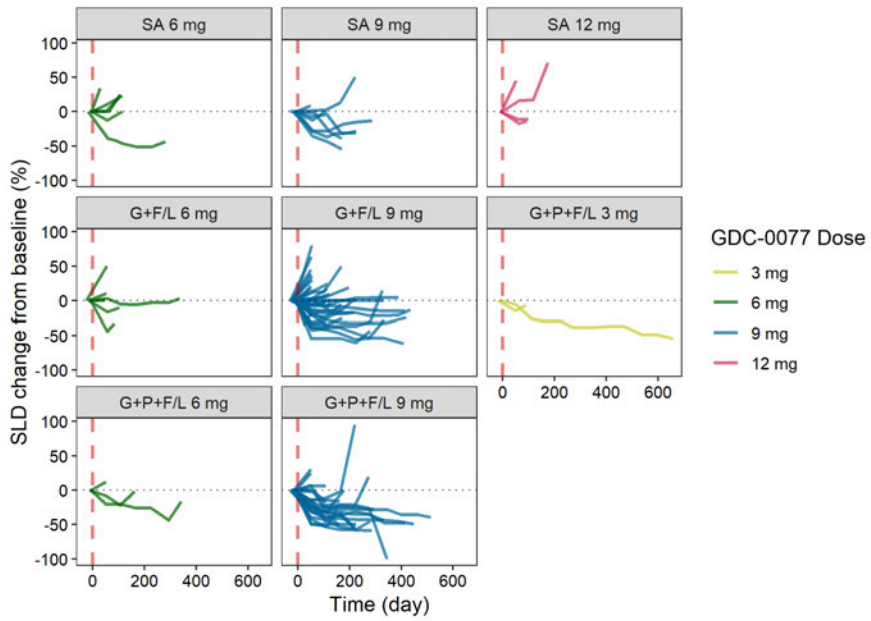


Clinical Cut-Off Date: March 29, 2019
Absolute change (left) and percent change from baseline (right) of SLD are presented.
G+F/L = GDC-0077 + Fulvestrant or Letrozole, G+P+F/L = GDC-0077 + Palbociclib + Fulvestrant or Letrozole, SA = GDC-0077 Single Agent, SLD = sum of longest diameters

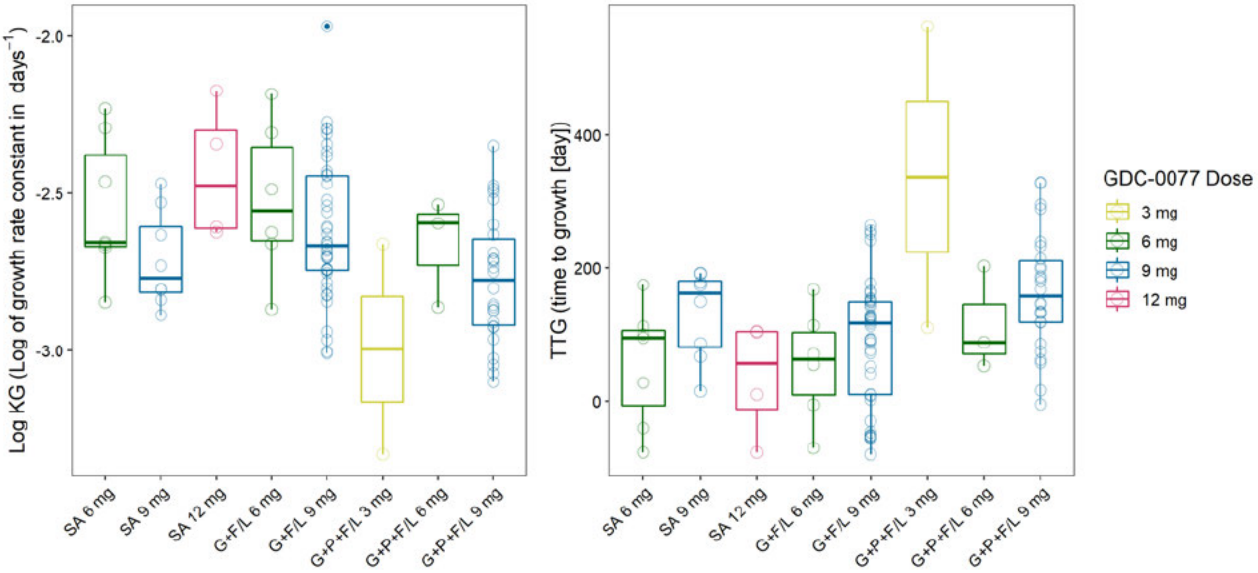
Two patients in Stage I Arm A (GDC-0077 single agent) at the 12 mg daily dose level experienced 1 DLT each and thus, 12 mg daily was considered not tolerable and data for this dose level are limited. The GDC-0077 single agent MTD was determined to be 9 mg daily and this dose was evaluated in combination with endocrine therapies letrozole and fulvestrant, with and without palbociclib, in the expansion stage of the study and thus, the majority of available data are at the 9 mg daily dose level. Limited data are available at 3 mg daily (only evaluated in

Arm B [GDC-0077 + palbociclib + letrozole]) and 6 mg daily (evaluated in Arms A [single agent], B [GDC-0077 + palbociclib + letrozole], and C [GDC-0077 + letrozole]) dose levels from the dose escalation stage only.
The empirical model to describe longitudinal tumor size published by Stein et al. (Stein W.D. et al., 2011) was improved by using nonlinear mixed effect modeling and by estimating the baseline;

$$TS(t_{ij}) = TS_{i,0} \times \left[e^{(KG_i \cdot t_{ij})} + e^{(-KS_i \cdot t_{ij})} - 1\right] + \varepsilon_{ij}$$
$$i = 1, 2, \ldots, n: individuals$$
$$j = 1, 2, \ldots, m: observations$$

where TS is the tumor size (SLD), KG is the growth rate constant, and KS is the shrinkage rate constant. Inter-individual variability was also taken into consideration as well as residual error represented by *e*. TGI metrics such as log(KG) and time to growth (TTG), reported as good predictor of long-term survival were derived (Bruno R et al 2014). The analysis was conducted by using NONMEM (version 7.4.3).

All the parameter estimates were obtained with good precision (RSE <30%). Figure 2 shows the summary of TGI metrics estimated for each individual based on the Phase I/Ib data.
Figure 2: Estimate TGI Metrics by Treatments Groups in Study GO39374



Log KG (left) and TTG (right) are presented. Each point represents the individual estimated TGI metrics for each patient. Box plot represent the 25th percentile, median, and 75th percentile values in each group, and upper and lower whisker displays a confidence interval.
G+F/L = GDC-0077 + Fulvestrant or Letrozole, G+P+F/L = GDC-0077 + Palbociclib + Fulvestrant or Letrozole, SA = GDC-0077 Single Agent, KG = growth rate constant, TTG = time to growth

Although the estimated TGI metrics are overlapping, 9 mg daily showed a better efficacy trend compared with 6 mg daily (slower tumor growth represented by smaller log(KG), longer

duration of response represented by larger TTG) consistently across single agent and combination treatments. Of note, one patient treated with GDC-0077 3 mg daily, palbociclib, and letrozole in Stage I Arm B experienced long time on study (>600 days). This subject made TGI metrics look better in GDC-0077 3 mg group, but the efficacy trend in this group remains inconclusive due to very limited data.

Together with the available safety data from the Phase I study, the sponsor believes this analysis supports that GDC-0077 9 mg daily demonstrates a favorable risk-benefit and is the optimal dose for the Phase III Study WO41554 in combination with palbociclib and fulvestrant based on the totality of available data from nonclinical and Phase I studies.

Discussion: We acknowledge the initial safety and preclinical data you have provided. We continue to recommend that you gather additional safety and dose-finding information prior to initiating your proposed trial, however, this is at your discretion. The safety of GDC-0077 in combination with palbociclib and fulvestrant will be a review issue.

Question 6: Does the agency agree that the primary efficacy endpoint of investigator-assessed PFS, supported by secondary endpoints as indicated, are adequate to assess the efficacy of GDC 0077 in combination with palbociclib and fulvestrant in the target patient population?

FDA Response to Question 6: If you choose the primary efficacy analyses to be PFS based upon local investigator assessment, you will need to have a sensitivity analysis based on blinded independent reviewers' assessment. Your protocol and SAP should provide details about sensitivity analysis regarding PFS. Please refer to Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.

As your trial is currently designed, if the PFS analyses does not reach statistical significance, results based on secondary endpoints, subgroups, or further analyses of the primary endpoint cannot result in an efficacy claim.

You should conduct an interim analysis of OS at your PFS analysis and allocate alpha accordingly, for example, use an O'Brien-Fleming efficacy boundary rule.

Company Response: The sponsor acknowledges and thanks the agency for the feedback regarding blinded independent review and efficacy claims.

With regard to OS, the sponsor plans to conduct the analysis at the time of the primary PFS analysis, although, the overall survival endpoint may not be met at this time due to an insufficient number of events. Thereafter, additional analyses of overall survival will be conducted at time points defined through study milestones, such as Health Authority interactions.

Discussion: We agree with your response and have no additional comments.

Question 7: Does the agency agree with the proposed methods of statistical analysis and Type 1 error control in the planned Phase III study?

FDA Response to Question 7: One interim analysis for futility is acceptable. We do not recommend the use of interim analyses for efficacy regarding PFS due to the ascertainment bias in determining a PFS advantage.

Your sample size is reasonable. Statistical analysis should only be conducted when 227 PFS events are observed and confirmed.

We will consider the randomized efficacy-evaluable population as the primary analysis population.

Company Response: The sponsor acknowledges and thanks the agency for the feedback regarding interim analyses and the number of PFS events necessary for statistical analysis. For provided additional clarification, the sponsor plans to conduct the primary analysis in the ITT population which was referred to as the efficacy-evaluable population in the Briefing Package.

Question 8: Does the agency agree with the proposed safety monitoring plan and risk mitigation strategy for the planned Phase III Study WO41554?

FDA Response to Question 8: Yes.

Company Response: The sponsor thanks the agency for the feedback and has no further comments. No further discussion is required.

Question 9: Does the agency agree that the proposed patient-reported outcome (PRO) endpoints, which are considered relevant to the HR+/HER2− breast cancer patient population, may provide additional clinical risk-benefit information in support of the primary endpoint?

FDA Response to Question 9: If patient-reported pain, function, HRQoL, and tolerability are to be considered for a *marketing claim of treatment benefit,* we strongly recommend a clear endpoint definition and formal statistical testing with adjustment for multiplicity.

For time to pain deterioration, we recommend using a 10 point numeric pain rating scale such as item 3 from the brief pain inventory. Such an NRS pain item can used as a single item. The pain scale from (b) (4) **which is why we advise against the use of this scale. Clearly pre-specify the pain endpoint (e.g., censoring rules) and pre-specify several sensitivity analyses to include differing change thresholds as well as confirmation versus unconfirmed time to pain deterioration events. To strengthen PRO time to deterioration results, please include a patient-reported analgesic log to document analgesic use.**

See Additional Comments.

Company Response: The sponsor acknowledges the agency's feedback and will replace the pain scale (b) (4) with the "worst pain" item from the BPI-SF as the endpoint used to assess time to pain deterioration. The pain endpoint is pre-specified and the

sponsor will include sensitivity analyses that include different thresholds for meaningful change, as well as definitions of deterioration (confirmed/definitive and unconfirmed). Documented analgesic use will be captured.

Please see company response below under Additional Comments regarding Patient Reported Outcomes.

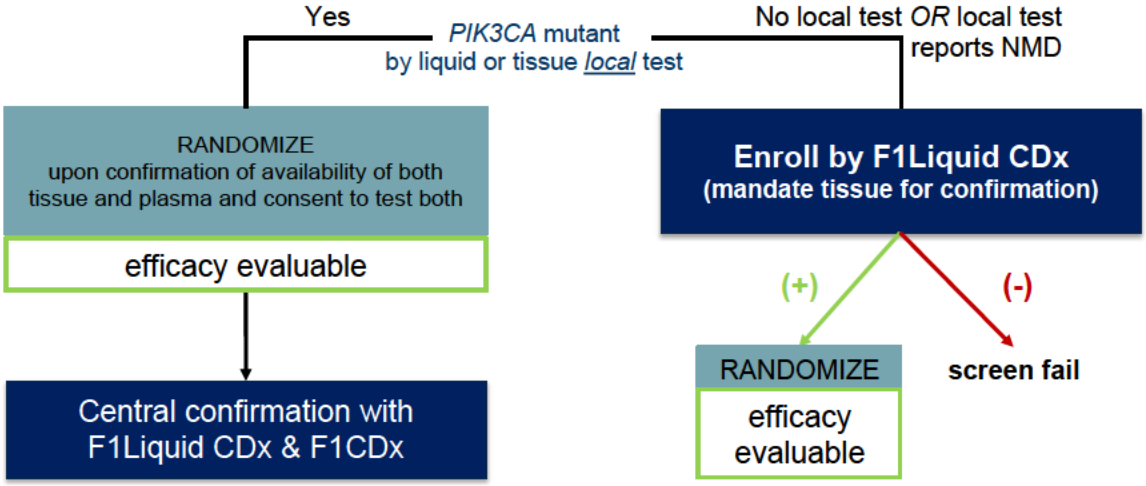
Discussion: You will submit your planned analgesic log for agency feedback.

Question 10: Does the agency agree with the enrollment of *PIK3CA*-mutation-positive patients through central testing with a blood-based Clinical Trial Assay (FoundationOne Liquid) or using pre-existing *PIK3CA* test results from a local laboratory?

FDA Response to Question 10: We agree that you can use a validated locked down central test, the FoundationOne Liquid assay, for enrolling PIK3CA mutation-positive patients in the trial.

Please see Additional Comments regarding our concerns with enrolling based on local laboratory tests.

Company Response: The sponsor acknowledges and thanks the agency for the feedback regarding enrollment of PIK3CA-mutation positive patients. The figure below outlines the sponsor's planned biomarker-focused enrollment strategy for the Phase III study.
Figure 3: Biomarker-Focused Enrollment Strategy



Please refer to the company responses under Additional Comments regarding CDRH Companion Diagnostic.

Discussion: **We acknowledge your planned biomarker focused enrollment strategy. You clarified that the patients will be enrolled based on the local blood and tissue-based assays and the central blood-based assay. You plan to obtain tissue samples for all enrolled patients. You will also monitor for discordance between plasma and tissue as well as central and local testing. You will potentially modify your biomarker enrollment strategy as this data evolves. Potential review issues include discordance between plasma and tissue testing as well as central and local testing.**

We note that you are planning a pre-submission to CDRH to discuss the analytical and clinical validation of the blood-based (b) (4) assay. It will be important to document with which test patients are determined eligible to enroll. Also document whether patients are enrolled following major protocol amendments.

Question 11: Does the agency agree that the proposed registrational package including the single Phase III study WO41554 and overall safety database would be sufficient to support full approval of GDC-0077 in combination with palbociclib and fulvestrant in the proposed indication?

FDA Response to Question 11: **Your proposed registrational package is reasonable. Whether your Phase 3 study would be sufficient to support full approval will be a review issue, and dependent on the clinical results of your study as well as the safety profile of GDC-0077 in combination with palbociclib and fulvestrant. In an add-on clinical design trial, a 3.3 month improvement in PFS with added toxicity is unlikely to represent a clinical benefit.**

Company Response: The sponsor thanks the agency for the feedback and has no further comments.

ADDITIONAL COMMENTS

QT prolongation

We do not have sufficient information to evaluate whether PK/ECG data from Study GO39374 would be adequate to characterize the QT prolongations risks of GDC-0077 in combination with palbociclib and fulvestrant. We encourage you to submit the QT assessment report for review.

Additionally, we have the following comments for you to consider:

1. **We encourage you to conduct by-timepoint analysis and categorical analysis on the expansion cohorts, especially the triple combination that will be tested in the Phase 3 study.**

2. **For exposure-response analysis, we recommend the analysis and reporting of results follow the recommendations described in "Scientific white paper on concentration-QTc modeling" (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2017; doi**

10.1007/s10928-017-9558-5) and "Correction to: Scientific white paper on concentration-QTc modeling" (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2018; doi 10.1007/s10928-017-9565-6).

3. **When you submit your QT study report, please include the following items:**

   a) **A completed Highlights of Clinical Pharmacology and Cardiac Safety Table**

   b) **Investigator's Brochure**

   c) **Clinical study protocol**

   d) **Statistical analysis plan**

   e) **Annotated CRF**

   f) **A data definition file which describes the contents of the electronic data sets**

   g) **Electronic data sets as SAS.xpt transport files and all the SAS codes used for the primary statistical and exposure-response analyses. The specifications is posted at the FDA Study Data Standards Resources webpage (https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources) under 'Technical Guides'. Please refer to this website for Technical Specifications before submitting reports for QT studies.**

   h) **Data set whose QT/QTc values are the average of the above replicates at each nominal time point**

   i) **Adverse Event analysis using the MedDRA SMQ "Torsade de pointes/QT Prolongation" and include the preferred term "Seizure" by treatment and dose level.**

   j) **Narrative summaries and case report forms for any**

      i. **Deaths**
      ii. **Serious adverse events**
      iii. **Episodes of ventricular tachycardia or fibrillation**
      iv. **Episodes of syncope**
      v. **Episodes of seizure**
      vi. **Adverse events resulting in the subject discontinuing from the study**

   k) **Study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed**

4. **Submit all related ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)**

Company Response: The sponsor acknowledges and thanks the agency for the feedback. The sponsor will take these recommendations into consideration and plan to prepare a QT assessment report and related items as specified above at the time of the NDA filing.

Patient Reported Outcomes

Inclusion of PRO data in the product label will depend on if your exploratory or secondary endpoint is included in the statistical hierarchy, the adequacy of submitted data, the strengths and limitations of the instrument within the given context of use, and the design and conduct of the trial. If not in the statistical hierarchy this will be a review issue and results will be considered descriptive.

A. PRO-CTCAE

1. Item Selection

Please provide a strong rationale for your unbiased selection of symptomatic side effects to assess including support from animal and clinical data where available. Side effects from both arms should be assessed in all patients in a multi-arm trial.

2. Assessment Frequency

To capture acute toxicities, symptomatic side effects should be assessed weekly for the first few cycles of treatment and then the frequency can be decreased depending on the trial context.

B. EORTC QLQ-C30

The EORTC QLQ-C30 is a widely used patient-reported outcome (PRO) instrument that is modular in its design, with individual symptom scales and items as well as global HRQL and 5 functional scales scored separately. This may facilitate modification when incorporating additional tools (e.g., PRO-CTCAE or PROMIS measures) in an overall PRO measurement strategy to adapt to specific disease and treatment contexts. We recommend you prioritize analyses of collected PRO data by the most important patient-reported symptoms and functional impacts (i.e., physical function) that are responsive to treatment.

Company Response:

A. PRO-CTCAE
The sponsor acknowledges the agency's feedback and would like to clarify the rationale for the specific items chosen from the PRO-CTCAE item bank. Only adverse events that are patient self-reportable (Basch et al. 2014) were selected for assessment in this study. Adverse events that rely on laboratory testing assessments (e.g., neutropenia, anemia) and that may frequently

present as being primarily asymptomatic or with nonspecific signs and symptoms were not included. Adverse events that did not have an identifiable symptom equivalent in the PRO-CTCAE were also excluded. Based on the above criteria, 7 symptomatic adverse events associated with either GDC-0077 preliminary safety data or published safety data from palbociclib or fulvestrant treatment were selected from the PRO-CTCAE item bank. These include diarrhea, nausea, vomiting, decreased appetite, fatigue, mouth sores, and rash symptoms. An additional question providing an overall assessment of the burden of side effects will also be collected. As the randomized study assesses the addition of GDC-0077 to the combination of palbociclib and fulvestrant, these selected items are believed to provide the greatest coverage of potential symptoms in both treatment groups while minimizing burden to patients by excluding items that may occur but less frequently.

The selected PRO-CTCAE items will be assessed bi-weekly during the first three cycles and then every other month thereafter. The sponsor's position is that this assessment frequency will adequately capture acute symptoms associated with study treatment while minimizing assessment burden for patients who may not be experiencing these symptoms.

B. EORTC QLQ-C30

The sponsor acknowledges the agency's feedback and plans to prioritize the following analyses based on impact and potential response to study treatment. Following the analysis of the "worst pain" item from the BPI-SF, analyses for the secondary endpoints related to the physical and role function scales and the GHS/QoL scale of the EORTC QLQ-C30 will be prioritized as highly relevant for this study population. The sponsor believes that based on the published literature with palbociclib in this population, these endpoints are also most likely to be responsive to treatment (Harbeck et al., 2016; Rugo et al., 2018).

CDRH Companion Diagnostic

Enrolling using local laboratory tests are known to present several challenges as follows:

- **You propose to enroll patients based on results from either testing performed at a central laboratory or based on available results from local tissue or plasma tests using local laboratory tests (LDTs). While the proposed local tests may identify the presence of PIK3CA, the performance of the different assays may not be comparable due to differences in the assays, platforms, or specimen types tested. Also, the different local tests and methodologies may not be adequately validated and as such, if different tests are utilized at the clinical sites, the different tests may not identify the same intent-to-treat (ITT) populations. We recommend that you enroll patients based on central testing.**

- **You also indicate that patients enrolled based on local test results need to provide both blood and tumor tissue specimens for confirmation of PIK3CA mutation status by a central investigational testing site. For patients enrolled based on tumor tissue results from LDTs, temporally matched blood samples may not be available to send for confirmatory testing. If temporally matched samples are not available, depending on the time between tumor tissue and plasma collection for patients**

tested locally, one sample may not be representative of the other sample or the patient's status at the time of enrollment. In addition, if blood was collected just prior to tumor tissue collection for local testing, there may be insufficient remaining plasma or stored ctDNA available for central testing. The ability to support a future CDx claim for the FoundationOne Liquid may be negatively affected if a large percentage of patients enrolled using tumor tissue results obtained from LDTs who are missing either blood specimens or temporally matched blood specimens. Please consider revising your inclusion criteria to include specifications for obtaining temporally or near-temporally matched samples.

- **Preanalytical conditions (e.g., blood-collection tube, sample processing and storage, ctDNA isolation methods, etc.) are known to have a profound effect of test performance. The plasma specimens may not be collected and processed in the same manner between local sites, which may result in discordances between the local and central testing site results. Therefore, we recommend that you try to assure that all blood samples are collected according to a pre-specified collection and handling protocol which is used at each site to minimize variability due to pre-analytic conditions and the protocol should be consistent with the specimen requirements for the FoundationOne Liquid assay.**

- **Therefore, we recommend that you consider enrolling all patients based on central tissue and plasma tests. If you choose to proceed with the proposed enrollment strategy, you should plan to use the same testing procedures (including specimen type, test method, NGS platform and bioinformatics pipeline etc.) to enroll patients. In addition, you should bank all samples used for enrollment by the local sites and also plan to collect a proportion of screen negative samples to be available for testing by the central investigative test(s) and attempt to obtain information regarding: the time the specimens were obtained; the specimen collection and handling conditions for the blood specimens, the test used to identify the mutations for enrollment as well as information regarding the test(s) analytical and clinical performance characteristics (e.g., limit of detection, analytical sensitivity, cut-offs, etc.). In addition, we recommend that you verify and use test results from sites whose tests are fully specified and have cutoffs that are locked down.**

- **If you are seeking a standalone claim for the blood-based test, you should ensure that the tissue to plasma concordance is high, the negative predictive value (NPV) should also be very high, i.e., the proportion of patients who are tissue negative among those that are plasma negative should be ~1. Also, the efficacy in the [plasma(+) tissue(+ or -)] and that of [tissue(+) plasma [(+ or -)] subgroups should be clinically and statistically significant and comparable.**

- **Lastly, as part of your statistical analysis plan, you should specify how you intend to address discordant results between the local test results and central test results and discordant results between the tumor tissue and plasma results, particularly for patients enrolled on tissue vs. ctDNA and vice versa.**

A. **Company Response:** The sponsor acknowledges the agency's feedback regarding the use of local tests as well as centralized FoundationOne Liquid testing to identify the intention-to-treat (ITT) population and would like to clarify the rationale for this strategy.

We propose to enable the use of local molecular test results for enrollment for the following reasons:

- Reduce time to treatment: Genomic testing for cancer-related alterations is becoming more common in clinical practice and, further, many large cancer treatment centers have implemented and/or have access to high-quality molecular tests that include the detection of alterations in PIK3CA (e.g., MSK-IMPACTTM). Therefore, allowing patients to enroll based on preexisting local test results is an effort to reduce time to treatment for patients with existing results.

- Hotspot PIK3CA mutations are early, truncal driver events: The PIK3CA mutations eligible for the study have been shown to be truncal, early events in tumor cells and are maintained throughout tumor evolution (Kalinsky, et al. Br Ca Res Treat, 2011). These alterations are robust and are generally detectable across multiple technologies and specimen types.

- High local to central test concordance for PIK3CA mutations in previous studies: Though the sample sizes are small, unpublished data from the PMT4979g basket study with taselisib (GDC-0032) and from the ongoing Study GO39374 with GDC-0077 in HR+/HER2- breast cancer show concordance between sites' local molecular tests and Foundation Medicine's ctDNA-based assays is ≥85% (PPA, positive predictive agreement). This supports our confidence in using local testing to detect PIK3CA hotspot alterations.

- sponsor will allow the use of only validated local tests and appropriately certified laboratories: For sites that propose to enroll patients based on a locally-available molecular test, the sponsor plans to provide a questionnaire to each site to assess the acceptability of the local molecular tests and testing laboratories prior to allowing patients to be considered for screening and enrollment. Acceptable tests must be performed in a CLIA-validated or equivalently certified laboratory, must have adequate coverage of PIK3CA, must be real-time PCR-based or NGS-based, and must meet additional assay validation and mutation reporting specifications. Local molecular tests that meet these criteria will be individually approved by the sponsor.

- Demographic balance: The sponsor plans to collect baseline demographic data on all screened patients in order to compare demographics among patients enrolling via a local molecular test versus those enrolling via the central FoundationOne Liquid assay.

Based on initial feasibility assessments, we anticipate that ~75% of our sites will not have access to validated local molecular tests and will enroll exclusively by the central FoundationOne Liquid assay. Additionally, all patients will be required to provide a baseline blood sample for the central FoundationOne Liquid assay. The sponsor plans to monitor local/central discordance and halt enrollment by local testing if the number of local test positive/central test negative patients reaches 60; this will allow the ITT population to be comprised of a minimum of 340 patients mutation positive by the central FoundationOne Liquid assay (≥ 85% of ITT).

B. The sponsor acknowledges the agency's feedback regarding the temporal collection of patient specimens. It is precisely due to this potential issue that the sponsor has chosen to enroll patients primarily based on blood (ctDNA) results rather than tumor tissue results. The blood sample at screening will be the most current and comprehensive reflection of the patient's tumor mutational status, whereas tumor tissue specimens may be significantly temporally distant from Study start for a patient, and represent only a 'snapshot' of the patient's overall tumor mutational landscape. Further, the Study protocol specifies that the tumor tissue specimen for central testing should be from the most recent metastatic biopsy whenever possible. Additionally, PIK3CA mutations are thought to be early and truncal oncogenic driver events that are likely to track over time in both tissue and in blood (Kalinsky, et al. Br Ca Res Treat, 2011). Therefore, these truncal/clonal hotspot mutations are more easily captured across platforms, timepoints, and assays with different sensitivities (Clark et al., J Mol Diag, 2018, Figure 6). This is supported through the ≥85% concordance (PPA) we observe between varied local tests for PIK3CA mutations and central blood-based Foundation Medicine assays (Studies PMT4979g and GO39374, referenced above).

C. See response above for CDRH comments 3B

D. While the sponsor agrees that it would be ideal for different sites to collect and process plasma specimens in the same manner, it is not possible for the sponsor to control the manner in which sites run their own local tests. However, the sponsor plans to collect detailed assay information on preanalytical conditions of samples collected and assayed with local tests in order to understand any possible discordance between local and central test results.

In the Laboratory Manual associated with the Study protocol, the sponsor will include detailed instructions regarding the collection volumes, tubes, processing, storage, and shipment conditions to ensure adequate and high-quality collections and enable downstream success of the FoundationOne Liquid assay. We will work closely with Foundation Medicine to ensure Study collection procedures are in accordance with Foundation Medicine's assay requirements. Furthermore, we are working with experienced laboratory and sample handling vendors to create sampling kits, complete with the optimal collection tubes and instructions, for sites participating in the study.

E. The sponsor thanks the agency for these recommendations to enable the proposed enrollment strategy. All FoundationOne Liquid central testing will be performed at the central testing site under strict specifications to ensure assay success.

   The sponsor cannot mandate local testing methods and procedures, but will collect information regarding the local test name and type, as well as sample collection time, sample handling conditions, and sample processing for any local tests.

   The sponsor plans to bank both blood and tissue samples used for enrollment from all patients, including those patients who screen-fail based on the central FoundationOne Liquid assay.

   As described above, the sponsor will assess the acceptability of local molecular tests based on strict validation, performance, and reporting criteria.

F. The sponsor plans to file a standalone blood-based CDx on the FoundationOne Liquid assay and seeks clarification from FDA regarding the need for high tissue to plasma concordance for this submission. A Pre-Submission to CDRH is planned to discuss the analytical and clinical validation of the assay.

(b) (4)

G. The sponsor acknowledges and thanks the agency for these recommendations, however, requests clarification as to whether the agency is referring to the statistical analysis plan (SAP) as part of the clinical trial protocol or to the SAP specific to CDx development that will be presented to CDRH in a Pre-Submission Meeting.

Discussion: The SAP mentioned in the additional comments refers to the diagnostic plan.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology

drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For the latest version of the molecular target list, please refer to https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm544641.htm.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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08/02/2019 09:15:31 AM

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