Phase I Dose-Escalation Study of Taselisib, an Oral PI3K Inhibitor, in Patients with Advanced Solid Tumors

Dejan Juric, Ian Krop, Ramesh K. Ramanathan, Timothy R. Wilson, Joseph A. Ware, Sandra M. Sanabria Bohorquez, Heidi M. Savage, Deepak Sampath, Laurent Salphati, Ray S. Lin, Huan Jin, Hema Parmar, Jerry Y. Hsu, Daniel D. Von Hoff, and José Baselga
ABSTRACT

Taselisib is a potent and selective tumor growth inhibitor through PI3K pathway suppression. Thirty-four patients with locally advanced or metastatic solid tumors were treated (phase I study, modified 3+3 dose escalation; 5 cohorts; 3–16 mg taselisib once-daily capsule). Taselisib pharmacokinetics were dose-proportional; mean half-life was 40 hours. Frequent dose-dependent, treatment-related adverse events included diarrhea, hyperglycemia, decreased appetite, nausea, rash, stomatitis, and vomiting. At 12 and 16 mg dose levels, dose-limiting toxicities (DLT) were observed, with an accumulation of higher-grade adverse events after the cycle 1 DLT assessment window. Pharmacodynamic findings showed pathway inhibition at ≥3 mg in patient tumor samples, consistent with preclinical PIK3CA-mutant tumor xenograft models. Confirmed response rate was 36% for PIK3CA-mutant tumor patients with measurable disease [5/14: 4 breast cancer (3 patients at 12 mg); 1 non–small cell lung cancer], where responses started at 3 mg, and 0% in patients with tumors without known PIK3CA hotspot mutations (0/15).

SIGNIFICANCE: Preliminary data consistent with preclinical data indicate increased antitumor activity of taselisib in patients with PIK3CA-mutant tumors (in comparison with patients with tumors without known activating PIK3CA hotspot mutations) starting at the lowest dose tested of 3 mg, thereby supporting higher potency for taselisib against PIK3CA-mutant tumors. Cancer Discov; 7(7); 704–15. ©2017 AACR.

See related commentary by Rodon and Tabernero, p. 666.

INTRODUCTION

In the three decades since the discovery of PI3K, the connection between cancer and PI3K has been substantiated (1). PI3K catalyzes the transformation of PIP2 to PIP3, involved in the phosphorylation of AKT and associated proteins in the AKT–mTOR pathway (2–4). Under normal physiologic conditions, the PI3K/AKT/mTOR pathway plays a central role in multiple cellular functions including angiogenesis, proliferation, survival, and metabolism. However, this same pathway turns tumorigenic through the accumulation of genetic aberrations in one or more of several key players, including those in the PI3K family kinase isomers. Among the PI3K family kinase isomers, the class I PI3K isomers are differentiated by their catalytic subunits: p110α, p110β, p110γ, or p110δ. Expression of the PI3Kα isoform can become deregulated through activating mutations or amplifications of the PIK3CA gene that encodes p110α. This has been established in several solid tumors, and with an especially high prevalence in cervical cancer (69%), squamous cell lung cancer (53%), head and neck cancer (32%), breast cancer (27%), and endometrial cancer (24%; ref. 5).

Results

Predicting Optimal Dose from a PIK3CA-Mutant Breast Model

Nonclinical studies had demonstrated that taselisib inhibited proliferation of p110α-mutant breast cell lines with an average IC_{50} of 70 nmol/L and inhibited tumor growth in human breast xenograft models harboring PIK3CA mutations (6). We conducted additional studies on growth inhibition in a PIK3CA-mutant breast cancer model to further assist in the identification of the optimal dose and schedule of taselisib in the phase 1 study. In nude mice bearing KPL-4 breast cancer xenografts that harbor a hotspot mutation (H1047R) in PIK3CA, daily oral dosing of taselisib at 0.20, 0.39, 0.78, 1.56, 6.25, and 25 mg/kg resulted in dose-dependent tumor growth inhibition and regressions (Fig. 1). Tumor volume traces of individual animals in each cohort demonstrated minimum variability in tumor growth inhibition and response (Supplementary Fig. S1). Taselisib was well tolerated with <10% body weight loss in tumor-bearing mice (data not shown). Moreover, robust PI3K pathway suppression in KPL-4 xenografts based on a significant reduction in levels

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of phosphorylated AKT (Supplementary Fig. S2A), PRAS40 (Supplementary Fig. S2B), and S6 ribosomal protein (Supplementary Fig. S2C) was observed following a single dose of taselisib when compared with vehicle-treated animals. Notably, suppression of the PI3K pathway in KPL-4 xenografts for up to 24 hours was observed following a single dose of 25 mg/kg taselisib, and was required for maximum efficacy (Supplementary Fig. S2A–S2C). The dose-dependent tumor growth inhibition observed in the KPL-4 model (Fig. 1) was used to estimate the taselisib dose expected to lead to efficacy against human tumors. The method utilized was previously described with the PI3K inhibitors pictilisib (GDC-0941) and apitolisib (GDC-0980; refs. 10, 11). The method combines pharmacokinetics/pharmacodynamics (PK/PD) modeling of the mouse efficacy data with the predicted human PK parameters (12). The dose in humans corresponding to the xenograft target tumor growth inhibition of 60%, as proposed by Wong and colleagues (13), was predicted to be 6 mg daily.

**Phase Ia Clinical Trial Design**

Dose escalation started at the 3 mg dose level and escalated up to 16 mg before testing of the final cohort at 12 mg (Fig. 2A and B) via a modified 3+3 design. Additional patients were evaluated in certain cohorts in order to replace dose-limiting toxicity (DLT) nonevaluable patients (e.g., due to disease progression) and to obtain additional safety data.

**Baseline Patient Demographics and Disease Characteristics**

From March 2011 to August 2012, 34 patients were enrolled at 3 sites in the United States. The cutoff date for analysis was July 30, 2014. The median treatment duration was 2 months (range, 0.03–15.67). Patients were representative of a heavily pretreated population with a median number of prior therapies of 4 (range, 2–13). Further details on the baseline demographics and disease characteristics are shown in Supplementary Table S1.

**Safety**

Adverse events (AE) observed with taselisib treatment were consistent with those observed with other PI3K inhibitors, including hyperglycemia, diarrhea, rash, and stomatitis (14, 15). No treatment-related grade ≥3 AEs were observed at the 3, 5, or 8 mg dose levels, so the next dose level tested was the 16 mg dose level. Two of 11 patients treated at 16 mg daily experienced AEs that qualified as a DLT. The first DLT was grade 4 hyperglycemia in a 63-year-old female with pancreatic cancer. The patient was admitted to the hospital on study day 14 and treated with pioglitazone, insulin, and saline hydration, and study drug was permanently discontinued. The event resolved the following day (study day 15). Although it is unclear whether the patient’s pancreatic cancer may have caused the patient to be more susceptible to hyperglycemia, this grade 4 hyperglycemia event was deemed a DLT per investigator. The second DLT was grade 3 fatigue in a 65-year-old female with breast cancer on study day 18. Dosing with study drug was held; the event resolved on study day 28. Although the patient did have some concurrent diarrhea, the grade 3 fatigue was deemed a DLT per protocol definition.

Although the 16 mg dose level did not technically exceed the MTD (≤33% of evaluable patients experiencing DLT), the high frequency of severe AEs that began after cycle 1 (days 1–35) made the 16 mg dose level not tolerable (Supplementary Table S2), and the next dose level tested was at a lower dose of 12 mg. One of 10 patients treated at the 12 mg dose level experienced an AE that qualified as a DLT. This patient had grade 3 acute renal failure secondary to concurrent grade 3 hyperglycemia. The acute renal failure resolved upon discontinuation of study drug and supportive care to treat the hyperglycemia. Of note, more than 6 patients were evaluated at the 12 mg and 16 mg cohorts in order to replace DLT nonevaluable patients (e.g., due to disease progression or patients not receiving adequate number of taselisib doses in the DLT window in cycle 1 to be evaluable) and to obtain additional safety data.

AEs related to taselisib, of any grade, were observed in 31 patients (91%), and of grade ≥3 in 14 patients (41%; Table 1). Grade ≥3 AEs that occurred at a frequency greater than 5% included hyperglycemia (15%), rash (12%), diarrhea (6%), fatigue (6%), and pruritus (6%). Other grade ≥3 AEs observed in 1 patient included colitis (confirmed via colonoscopy), pneumonitis, lung infection, acute renal failure, skin exfoliation, and stomatitis. The only treatment-related grade ≥4 AE was hyperglycemia as described above. AEs regardless of attribution are provided in Supplementary Tables S3 and S4.

AEs related to taselisib were monitorable, manageable, and reversible. AEs of rash, colitis, and pneumonitis resolved upon holding study drug medication and administration of topical and/or systemic corticosteroids. The grade 3 colitis AE observed had a later onset and occurred on day 160 of
The group mean time profiles and the dose proportionality for taselisib following single and multiple daily oral doses in cycle 1 and summary of PK parameters are presented in Table 2 and Supplementary Fig. S4A–S4D. After a single dose, the cohort mean half-life ($t_{1/2}$) ranged from 36.7 to 43.8 hours with mean $t_{1/2}$ of approximately 40 hours. The apparent clearance (CL/F) ranged from 4,750 to 9,170 mL/hr. After 8 daily doses, the apparent clearance at steady state (CLss/F) ranged from 4,320 to 9,150 mL/hr. Taselisib exposures, as measured by $C_{\text{max}}$ and $AUC_{0-24}$, were approximately dose proportional with a 2- to 4-fold accumulation and moderate variability in $C_{\text{max}}$ and $AUC_{0-24}$. No apparent time-dependent PK exposure was observed.

Pharmacodynamic Modulation of the PI3K Pathway

Decreased $^{18}$F fluorodeoxyglucose (FDG) uptake in tumor sites, consistent with PD modulation of glucose metabolism, has been observed in other trials with PI3K inhibitors and is considered to be a PD marker of PI3K inhibition given the important role that PI3K plays in cellular glucose uptake (14, 15). Partial metabolic responses (PMR) with FDG–PET imaging were observed in 70% of patients (16/23 evaluable patients), including at the lowest dose tested of 3 mg daily (Fig. 3). There is a trend of a dose response, but the small number of patients per dose level does not provide sufficient data to be conclusive. PMRs were observed across multiple tumor types, including lung, breast, head and neck, ovarian, endometrial, and adnexal cancers. PMRs were observed in patients both with $PIK3CA$-mutant tumors (82%; 9 of 11) and with tumors without known activating $PIK3CA$ hotspot mutations (66%; 7 of 11; Fig. 4A–C).
Fresh paired tumor biopsies were obtained from 5 patients enrolled onto study and were fixed in optimal cutting temperature compound. Of the 5 paired biopsies, 2 patients with non–small cell lung cancer (NSCLC) had tumor content in both the pretreatment and on-study biopsies, and were evaluated by reverse phase protein array (RPPA) for PI3K pathway PD markers, including phospho-AKT (pAKT; Fig. 5A and B). Decreases greater than 60% in pAKT and pS6 (compared with baseline biopsies) were demonstrated in these patients, who were treated with taselisib at doses of 3 mg and 16 mg once daily, respectively.

As inhibition of the PI3Kα isoform is thought to alter glucose metabolism and result in hyperglycemia, the observation of increased frequency and severity of hyperglycemia at higher doses of taselisib is also supportive of significant inhibition of the PI3K pathway.

### Table 1. Treatment-related AEs in ≥5% of patients and AEs of grade 3 or higher

<table>
<thead>
<tr>
<th></th>
<th>3 mg (n = 6)</th>
<th>5 mg (n = 3)</th>
<th>8 mg (n = 4)</th>
<th>12 mg (n = 10)</th>
<th>16 mg (n = 11)</th>
<th>All (N = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse events in ≥5% of patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of patients with ≥1 AE</td>
<td>6 (100%)</td>
<td>2 (66.7%)</td>
<td>3 (75%)</td>
<td>10 (100%)</td>
<td>10 (90.9%)</td>
<td>31 (91.2%)</td>
</tr>
<tr>
<td>Total number of AEs</td>
<td>17</td>
<td>7</td>
<td>7</td>
<td>80</td>
<td>115</td>
<td>226</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (16.7%)</td>
<td>1 (33.3%)</td>
<td>1 (25.0%)</td>
<td>5 (50.0%)</td>
<td>7 (63.6%)</td>
<td>15 (44.1%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (33.3%)</td>
<td>1 (33.3%)</td>
<td>1 (25.0%)</td>
<td>5 (50.0%)</td>
<td>5 (45.5%)</td>
<td>14 (41.2%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1 (16.7%)</td>
<td>1 (33.3%)</td>
<td>1 (25.0%)</td>
<td>5 (50.0%)</td>
<td>5 (45.5%)</td>
<td>13 (38.2%)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>0</td>
<td>0</td>
<td>2 (50.0%)</td>
<td>3 (30.0%)</td>
<td>8 (72.7%)</td>
<td>13 (38.2%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (33.3%)</td>
<td>1 (33.3%)</td>
<td>1 (25.0%)</td>
<td>3 (30.0%)</td>
<td>6 (54.5%)</td>
<td>13 (38.2%)</td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6 (60.0%)</td>
<td>4 (36.4%)</td>
<td>10 (29.4%)</td>
</tr>
<tr>
<td>Rash†</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (30.0%)</td>
<td>3 (27.3%)</td>
<td>6 (17.6%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>0</td>
<td>0</td>
<td>4 (36.4%)</td>
<td>5 (14.7%)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (20.0%)</td>
<td>1 (9.1%)</td>
<td>3 (8.8%)</td>
</tr>
<tr>
<td>Pruritis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (30.0%)</td>
<td>0</td>
<td>3 (8.8%)</td>
</tr>
<tr>
<td>Colitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (10.0%)</td>
<td>1 (9.1%)</td>
<td>2 (5.9%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (18.2%)</td>
<td>2 (5.9%)</td>
</tr>
<tr>
<td>Mood altered</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (5.9%)</td>
</tr>
<tr>
<td>Neuropathy peripheral</td>
<td>1 (16.7%)</td>
<td>0</td>
<td>0</td>
<td>1 (10.0%)</td>
<td>0</td>
<td>2 (5.9%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (18.2%)</td>
<td>2 (5.9%)</td>
</tr>
</tbody>
</table>

| **Adverse events of ≥grade 3** |                        |             |             |               |               |             |
| Total number of patients with ≥1 AE | 0           | 0           | 0           | 6 (60.0%)     | 8 (72.7%)     | 14 (41.2%)  |
| Total number of AEs    | 0           | 0           | 0           | 13            | 16            | 29          |
| Hyperglycemia          | 0           | 0           | 0           | 2 (20.0%)     | 3 (27.3%)     | 5 (14.7%)   |
| Rash†                 | 0           | 0           | 0           | 3 (30.0%)     | 1 (9.1%)      | 4 (11.8%)   |
| Diarrhea              | 0           | 0           | 0           | 0             | 2 (18.2%)     | 2 (5.9%)    |
| Fatigue               | 0           | 0           | 0           | 0             | 2 (18.2%)     | 2 (5.9%)    |
| Pruritis              | 0           | 0           | 0           | 2 (20.0%)     | 0             | 2 (5.9%)    |
| Pneumonitis           | 0           | 0           | 0           | 0             | 1 (9.1%)      | 1 (2.9%)    |
| Colitis               | 0           | 0           | 0           | 1 (10.0%)     | 0             | 1 (2.9%)    |
| Exfoliative rash      | 0           | 0           | 0           | 0             | 1 (9.1%)      | 1 (2.9%)    |
| Lung infection        | 0           | 0           | 0           | 0             | 1 (9.1%)      | 1 (2.9%)    |
| Renal failure acute   | 0           | 0           | 0           | 1 (10.0%)     | 0             | 1 (2.9%)    |
| Skin exfoliation      | 0           | 0           | 0           | 0             | 1 (9.1%)      | 1 (2.9%)    |
| Stomatitis*           | 0           | 0           | 0           | 1 (10.0%)     | 0             | 1 (2.9%)    |

*Stomatitis includes the following terms: stomatitis, mucosal inflammation, lip ulceration.
†Rash includes the following terms: rash, rash erythematous, rash maculopapular.

### Biomarker Profiling of Patient Tumors

Tumor tissue and/or plasma were available from 30 and 33 of the 34 enrolled patients, respectively, for determination of PIK3CA mutation status. Fifteen of 34 patients were identified as having PIK3CA-mutant tumors, including 13 of 15 who were classified as PIK3CA mutant based on tissue, with 3 patients also harboring a KRAS mutation. One patient with colorectal cancer harbored both an AKTI and a KRAS mutation. Circulating tumor DNA (ctDNA) analysis from plasma identified the other 2 of 15 patients with PIK3CA-mutant tumors: For one, tumor tissue was without known activating PIK3CA hotspot mutations; for the other, no tissue was available. The tissue wild-type, plasma-positive PIK3CA-mutant patient was a patient with HER2+ metastatic breast cancer; tissue and plasma samples...
Taselisib in Refractory Solid Tumors

Table 2. PK parameters of taselisib (GDC-0032)

<table>
<thead>
<tr>
<th>Cohort (dose)</th>
<th>N</th>
<th>Cmax (μmol/L)</th>
<th>AUC0–24hr (μmol•L•hr)</th>
<th>AUCinf (μmol•L•hr)</th>
<th>CL/F (mL/hr)</th>
<th>t1/2 (hr)</th>
<th>Vz/F (L)</th>
<th>N</th>
<th>Cmax (μmol/L)</th>
<th>AUC0–24hr (μmol•L•hr)</th>
<th>AUCinf (μmol•L•hr)</th>
<th>CL/F (mL/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1 (3 mg)</td>
<td>6</td>
<td>0.0256 (37%)</td>
<td>4 (3–8) 0.441 (32%)</td>
<td>1.48 (33%)</td>
<td>4770 (29%)</td>
<td>43.8 (26%)</td>
<td>301 (45%)</td>
<td>6</td>
<td>0.111 (65%)</td>
<td>3 (2–4) 0.046 (48%)</td>
<td>1.79 (55%)</td>
<td>4320 (37%)</td>
</tr>
<tr>
<td>Cohort 2 (5 mg)</td>
<td>3</td>
<td>0.0304 (40%)</td>
<td>8 (3–8) 0.547 (43%)</td>
<td>1.64 (54%)</td>
<td>9170 (77%)</td>
<td>40 (48%)</td>
<td>433 (39%)</td>
<td>3</td>
<td>0.091 (53%)</td>
<td>3 (2–4) 0.042 (49%)</td>
<td>1.49 (49%)</td>
<td>9150 (64%)</td>
</tr>
<tr>
<td>Cohort 3 (8 mg)</td>
<td>4</td>
<td>0.0764 (43%)</td>
<td>4 (2–4) 1.342 (34%)</td>
<td>3.47 (15%)</td>
<td>5070 (13%)</td>
<td>38.2 (32%)</td>
<td>277 (38%)</td>
<td>3</td>
<td>0.188 (63%)</td>
<td>3 (2–4) 0.098 (55%)</td>
<td>3.21 (49%)</td>
<td>6310 (44%)</td>
</tr>
<tr>
<td>Cohort 5 (12 mg)</td>
<td>10</td>
<td>0.127 (42%)</td>
<td>3 (1–8) 1.8 (35%)</td>
<td>4.00 (30.5%)</td>
<td>4750 (77%)</td>
<td>36.7 (20%)</td>
<td>267 (81%)</td>
<td>10</td>
<td>0.302 (31%)</td>
<td>4 (2–4) 0.128 (36%)</td>
<td>5.1 (40%)</td>
<td>4810 (61%)</td>
</tr>
<tr>
<td>Cohort 4 (16 mg)</td>
<td>11</td>
<td>0.134 (39%)</td>
<td>4 (2–24) 2.26 (37%)</td>
<td>6.36 (48%)</td>
<td>6640 (45%)</td>
<td>39.7 (20%)</td>
<td>372 (45%)</td>
<td>9</td>
<td>0.441 (52%)</td>
<td>4 (2–8) 0.241 (76%)</td>
<td>8.1 (57%)</td>
<td>5440 (61%)</td>
</tr>
</tbody>
</table>

NOTE: PK parameters were reported as cohort mean (%CV), except for Tmax, which was reported as cohort median (range). Abbreviations: AUC0–24hr, area under the plasma concentration–time curve from 0 to 24 hours after dose; AUCinf, area under the plasma concentration–time curve from time 0 to infinity; CL/F, apparent clearance; Cmax, highest observed plasma concentration; Cmin, minimum concentration during the dosing interval; t1/2, terminal half-life; Tmax, time of maximum observed concentration; Vz/F, apparent terminal phase distribution volume.

were collected approximately 11 months apart. Two patients had complete loss of PTEN, and 3 were classed as PTEN-low (defined in Methods). Two of the PTEN-low tumors also contained a coexisting PIK3CA mutation.

Tumor Responses Observed with Taselisib Treatment

Thirty-two of 34 enrolled patients had baseline measurable disease. Of the 32 patients, 14 had PIK3CA-mutant tumors, 15 had tumors negative for the PIK3CA mutation, and the status was unknown for 3 patients. For the 29 patients with known PIK3CA mutation status, tumor response evaluation by FDG–PET was available for 23 patients (Fig. 4A) and by radiographic measurements [sum of longest diameter (SLD)] for 28 patients (Fig. 4B); the corresponding genetic profiles of the 28 patients with SLD data are presented (Fig. 4C).

The RECIST-confirmed response rate was 36% for those with PIK3CA-mutant tumors (5/14), and 0% in patients without known activating PIK3CA hotspot mutations (0/15). Of the 5 patients who responded, 4 had breast cancer and 1 had NSCLC with duration of objective response lasting 5.2 months (range, 2.8–13.5). Of the 5 patients with confirmed partial responses, all had tumors with mutations in the kinase domain (residue H1047) in the PIK3CA gene (Fig. 4). Confirmed partial responses were observed at doses including 3 mg [n = 1; NSCLC, H1047(Y)], 5 mg [n = 1; breast, H1047R], and 12 mg (n = 3; all breast cancer with H1047R). Although no confirmed partial responses were observed in the 4 patients with helical domain PIK3CA mutations, 1 patient with breast cancer had an unconfirmed response (~30.5% change from baseline), and 2 patients had tumor shrinkage (~11.4% and ~19.9% change from baseline). The fourth patient was a patient with colorectal cancer with a concurrent KRAS mutation who had progressive disease as his/her best response. In total, we enrolled 6 patients that had a KRAS hotspot mutation detected in either tumor tissue or ctDNA. For these 6 patients, 2 had a concurrent PIK3CA mutation and 4 had an undetectable PIK3CA mutation. Four of the 6 patients with KRAS-mutant tumors experienced progressive disease as their best clinical response, and 2 patients with KRAS-mutant tumors experienced stable disease as their best clinical response. Of the 2 patients whose tumor was PTEN-null, both patients experienced progressive disease as their best clinical response.

Figure 3. Percentage change from baseline in target lesion by FDG-PET in patients in different dose cohorts.

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Figure 4. A, Best FDG–PET response (mean percentage change in SUV\textsubscript{max}). PMR was defined as greater than a 20% decrease in %ΔSUV\textsubscript{max}. Patients with NA (not applicable) did not have subsequent scan after starting treatment. All patient data arranged in A are in the same patient order as in B and C. B, Best percent change from baseline in the SLD for target lesions via RECIST v1.1 available for 28 measurable patients with at least one post-baseline tumor assessment for target lesion (from 29 patients with baseline measureable disease) out of 34 enrolled patients. C, Corresponding somatic mutation profiling in both tumor- and plasma-extracted DNA from enrolled patients. The patient with PIK3CA mutation type “PIK3CA other” had an R88Q mutation.
**DISCUSSION**

Taselisib was dosed in patients from 3 to 16 mg, administered once daily. One of 10 patients treated at 12 mg and 2 of 11 patients treated at 16 mg experienced AEs that qualified as DLTs. Although 16 mg did not exceed the MTD as defined by DLTs in cycle 1, no higher dose beyond 16 mg was tested based upon the overall tolerability of taselisib that included assessment of the frequency/severity of AEs outside of the DLT window. Patients treated at the higher doses (12–16 mg) experienced increased frequency of fatigue and hyperglycemia.

The overall AE profile for taselisib in the current study was largely consistent with other PI3K inhibitors (14–16). Buparlisib (BMK120), a pan-class inhibitor that targets all four isomers of PI3K, had rash, hyperglycemia, diarrhea, and mucositis as frequent treatment-related AEs (14). In-class toxicities for pictilisib, another pan-class PI3K inhibitor, included diarrhea, hyperglycemia, rash, and pneumonitis (15). Colitis observed with taselisib is similar to that reported with idelalisib, a PI3Kδ isofrom-specific inhibitor approved for the treatment of hematologic malignancies (17), and is associated with a delayed-onset diarrhea that requires systemic corticosteroid treatment. Therefore, taselisib data are consistent with a possible mechanism of PI3Kδ isoform inhibition being involved in colonic inflammation. With pneumonitis, however, it is unclear which PI3K isoform is responsible for the AE, for pneumonitis has been observed in patients treated with pan-class I inhibitors and with taselisib (14–16).

Taselisib was rapidly absorbed ($T_{\text{max}} \approx 2–4$ hours) and demonstrated dose-linear and time-independent PK with moderate PK variability. The single-dose half-life was approximately 40 hours, enabling daily dosing with adequate drug exposure to suppress the PI3K signaling pathway. Evidence of PD target inhibition was observed in paired tumor biopsies as assessed by RPPA analysis of key signaling markers downstream of PI3K. We also observed decreased expression of pERK from inhibition being involved in oncogenic signaling pathways. Inhibition of PI3K signaling has been shown to activate MAPK signaling at early time-points through receptor tyrosine kinase activation (18, 19). However, sustained MAPK activation has also been shown to negatively regulate

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**Figure 5.** PD modulation of the PI3K pathway. Needle core tumor biopsies obtained from patients at baseline and at steady state (cycle 1, between days 15 and 21) were fixed and evaluated by RPPA for PI3K-AKT pathway markers. Decreases of $>60\%$ in pAKT and pS6, and up-phosphorylation of BIM (proapoptotic protein) were demonstrated in comparison between days 15 and 21 were fixed and evaluated by RPPA for PI3K-AKT pathway markers. Decreases of $>60\%$ in pAKT and pS6, and up-phosphorylation of BIM (proapoptotic protein) were demonstrated in comparison baseline for (A) patient 1 on 3 mg daily taselisib with paired biopsies from right upper anterior thigh mass and (B) patient 2 on 16 mg daily taselisib with paired biopsies from right upper anterior thigh mass.

**Examples of Tumor Responses in Patients with PIK3CA-Mutant Breast Cancer**

PMRs via FDG–PET (Fig. 4) and confirmed partial responses via RECIST (Fig. 4) established promising antitu-
pERK activity through dual-specificity phosphatases (DUSP) in receptor tyrosine kinase–activated cells (20). Interestingly, the two tumor biopsies analyzed in this study were NSCLC tumors, one of which contained an activating \( EGER \) exon 19 deletion mutation. FDG–PET responses were also observed in patients, consistent with PI3K-dependent inhibition of glucose metabolism.

PD modulation as shown by FDG–PET responses and paired tumor biopsies occurred in the first cohort tested at the 3 mg dose level, consistent with robust inhibition of the PI3K pathway. Although preclinical experiments have predicted that an exposure corresponding to the 6 mg dose level would be the minimal efficacious dose, in this phase Ia trial, we observed antitumor activity and PI3K pathway knockdown starting at the 3 mg dose in the first cohort. Four of 5 patients with tumor partial responses also had FDG–PET responses; the fifth patient did not have FDG–PET data.

Single-agent antitumor activity by CT scan was observed in 5 patients receiving 3 to 12 mg taselisib. All responses observed were in \( PIK3CA \)-mutant tumors. Based upon preclinical data, taselisib is expected to be active against tumors with either helical or kinase domain mutations. Confirmed partial responses were observed in patients with \( PIK3CA \) kinase domain mutations. There were fewer patients enrolled with helical domain mutations \((n = 4)\). One patient with breast cancer with a helical domain mutation did have an unconfirmed response (ES54SK), 2 patients had tumor shrinkage, and the fourth patient was a patient with colorectal cancer with a concurrent \( KRAS \) mutation which may render tumors relatively resistant to PI3K inhibitors. Three of the confirmed partial responses were observed at the 12 mg dose level.

The increased antitumor response in patients with \( PIK3CA \)-mutant cancer in this study as compared with prior PI3K inhibitors tested in the clinic may be due to several factors. One possible reason could be an increased therapeutic index for taselisib in patients with \( PIK3CA \)-mutant tumors. Taselisib has increased potency against the mutant version of the \( PI3K \) \( \alpha \) isoform, as demonstrated in chemical assays as well as in cancer cell lines (6). A higher therapeutic window due to greater selectivity for \( PIK3CA \)-mutant isoforms has been shown in extensive laboratory studies (21) and is also suggested by the fact that partial responses were observed only in patients with \( PIK3CA \)-mutant tumors. The other indirect evidence for an enhanced therapeutic window is that at the chosen recommended dose, patients were able to stay on the study agent for prolonged periods of time. In contrast, with pan-PI3K inhibitors, the majority of patients had to discontinue the study agent due to lack of tolerability (22, 23). Of note also, because taselisib inhibits the \( PI3K \) \( \alpha \) isoform 30-fold less than the \( PI3K \) \( \alpha \) isoform, the decreased antitumor activity against PTEN-null tumors is consistent with the observation that PTEN signals through \( PIK3CB \) (24). Others reported that acquired resistance to the alpha-selective \( PI3K \) inhibitor alpelisib (BLY-719) can occur through loss of PTEN expression (25). Recent phase I clinical data with alpelisib and letrozole showed increased clinical benefit rate in patients with \( PIK3CA \)-mutant tumors (26). We also did not observe any clinical responses in taselisib-treated patients whose tumors contained a \( KRAS \) mutation. This is consistent with the observation that cell lines harboring somatic alterations in \( RAS \)/RAF genes are insensitive to the pan-PI3K inhibitor pictilisib (27).

Taselisib exhibited a favorable safety profile and early signs of promising activity, especially in tumors that have activating mutations in \( PIK3CA \). Further studies as a single agent are ongoing. Given that approximately 40% of \( ER^+ \) breast cancers harbor the \( PIK3CA \) mutation, and given the extensive cross-talk between the ER and the PI3K signaling pathways (28), there is a strong rationale to evaluate taselisib in combination with endocrine therapy. Based upon these promising phase Ia data showing antitumor activity in the first cohort tested as well as subsequent phase Ib/II data of taselisib in combination with fulvestrant (29, 30), an ongoing randomized phase III study is testing taselisib plus fulvestrant in postmenopausal women with \( ER^+ \) metastatic breast cancer, with enrollment being enriched for patients with \( PIK3CA \)-mutant tumors (SAND-PIPER; clinicaltrials.gov NCT02340221).

**METHODS**

**In Vivo Efficacy**

All in vivo efficacy and PD studies were approved by Genentech and the Institutional Animal Care and Use Committee and adhered to the NIH Guidelines for the Care and Use of Laboratory Animals. The human KPL-4 breast cancer cell line was obtained from J. Kurebayashi (Kawasaki Medical School, Kurashiki, Okayama, Japan) in August 2006. The cell line was established from the malignant pleural effusion of a patient with breast cancer with an inflammatory skin metastasis. Cells were authenticated by short tandem repeat fingerprinting within 6 months of engraftment into mice for efficacy and PK/PD studies as described. KPL-4 cells, resuspended in 50% phenol red–free Matrigel (Becton Dickinson Bioscience) and Hank’s Balanced Salt Solution, were inoculated into 100 SCID beige mice (Charles River Laboratory) in the number 2/3 mammary fat pad. Each mouse was injected with \( 3 \times 10^6 \) cells. Tumors were monitored until they reached a mean tumor volume of 150 to 200 mm³. Tumor volume was measured using Ultra Cal-IV calipers (Model 54-10-111; Fred V. Fowler Co.). The following formula was used in Excel, version 11.2, to calculate tumor volume: Tumor Volume (mm³) = (Length \( \times \) Width \( \times \) Depth) \( \times \) 0.5. Mice were distributed into 7 groups of 8 mice based on tumor volume of 100 \( \mu \)l. Tumors were euthanized. A mixed modeling approach was used to analyze the repeated measurement of tumor volumes from the same animals over the course of the study. Mouse body weights were also recorded twice weekly over the course of the study. Mouse body weights were also recorded twice weekly. Mice whose tumor volume exceeded 2,000 mm³ or whose body weight loss was 20% of their starting weight were promptly euthanized. A mixed modeling approach was used to analyze the repeated measurement of tumor volumes from the same animals over time (31). This approach addresses both repeated measurements and modest dropouts due to any non–treatment-related death of animals before study end. Cubic regression splines were used to fit a nonlinear profile to the time courses of log tumor volume at each dose level. These nonlinear profiles were then related to dose within the mixed model. Tumor growth inhibition as a percentage of vehicle control (%TGI) was calculated as the percentage of the area under the fitted curve (AUC) for the respective dose group per day in relation to the
PI3K Inhibitor Taselisib in Refractory Solid Tumors

Pharmacodynamic Marker Analysis in KPL-4 Tumor Xenografts

Human KPL-4 cells, resuspended in 50% phenol red–free Matrigel (Becton Dickinson Bioscience) and Hank’s Balanced Salt Solution, were inoculated into 80 SCID beige mice in the number 2/3 mammary fat pad. Each mouse was injected with 3 × 10^6 cells. Tumors were monitored until they reached a mean tumor volume of 350 to 400 mm^3, after which mice were treated with a single oral dose of vehicle (0.5% methylcellulose/0.2% Tween-80) or 1, 5, and 25 mg/kg of taselisib for 1, 4, 8, 24, and 48 hours (n = 4 tumor-bearing animals for each dose and time-point). Following drug treatment, tumors were harvested, snap-frozen in liquid nitrogen, and processed for protein extraction using a buffer (Invitrogen) containing 10 mmol/L Tris, pH 7.4, 100 mmol/L NaCl, 1 mmol/L EDTA, 1 mmol/L EGTA, 1 mmol/L NaF, 20 mmol/L Na_3VO_4, 1% Triton X-100, 10% glycerol, 0.1% SDS, and 0.5% deoxycholate supplemented with a phosphatase and protease inhibitor cocktail (Sigma). Tumors were dissociated with a small pestle (Kontes Glass Company) in extraction buffer, sonicated briefly on ice, and centrifuged at maximum RPM for 20 minutes at 4°C. Protein concentrations were determined using the BCA Protein Assay Kit (Pierce). The Meso Scale Discovery Multi-Spot Biomarker Detection System (Meso Scale Discovery) was used to determine the levels of AKT, AKT phosphorylated at serine 473 (pAKT), S6RP, and S6RP phosphorylated at serine 235/236 (pS6RP). PRAS40 and PRAS40 phosphorylated at threonine 246 (pPRAS40) were detected using a validated LC/MS-MS assay on day 8 of cycle 1, and predose, 0.5, 1, 2, 3, 4, and 8 hours after dose administration was discontinued in patients who experienced disease progression or unacceptable toxicity.

Study Treatment

Taselisib (Genentech, Inc.) was taken on an empty stomach as a single dose (powder-in-capsule formulation) at the same time of day ± 2 hours (33). The dose for each patient was dependent on the dose level assignment.

Safety

Safety was evaluated by incidence, nature, severity, and relatedness of AEs, and graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0. All AEs regardless of attribution were collected until 30 days following the last administration of treatment or study discontinuation/termination, whichever was later. DLTs were defined as drug-related AEs observed during cycle 1 (days 1–35) and included any grade ≥ 3 nonhematologic toxicity with the exception of grade 3 diarrhea, nausea, or vomiting that responded to standard-of-care therapy. Hematologic toxicities defined as a DLT included grade ≥ 4 thrombocytopenia or grade ≥ 4 neutropenia (absolute neutrophil count <500/μL) lasting >5 days or accompanied by fever. Fasting grade ≥ 4 hyperglycemia, fasting grade ≥ 3 hyperglycemia for ≥ 1 week despite adequate trial of oral antihyperglycemic therapy, grade ≥ 3 fasting hyperchloremia or triglyceridemia for ≥ 2 weeks despite intervention with lipid-lowering agent, or grade ≥ 3 serum bilirubin or hepatic transaminase (alanine aminotransferase or aspartate aminotransferase) were considered DLTs. For patients with bone or liver metastases and baseline levels of ≤ 5 upper limit of normal (ULN) hepatic transaminase or alkaline phosphatase, level of > 10x ULN was considered a DLT. The MTD was defined as the highest dose at which <33% of patients developed a DLT during the DLT assessment window.

Pharmacokinetics

Taselisib PK was evaluated based on collection of serum samples during cycle 1 at predose, 0.5, 1, 2, 3, 4, 8, 24, 48, and 72 hours after dose. Additional samples were collected at predose, 2 hours after dose on day 8 of cycle 1, and predose, 0.5, 1, 2, 3, 4, and 8 hours after dose on day 15 of cycle 1. Predose and postdose samples were also collected on days 22 and 29 of cycle 1, then on day 1 of every cycle thereafter. Taselisib concentration was determined using a validated LC/MS-MS analytical procedure (Couvance Laboratories; ref. 34). The lower limit of quantification was 0.87 nmol/L. The PK assessment from patients was performed for cycle 1 plasma concentration–time data using standard noncompartmental (NCA) PK methods in WinNonlin (Version 5.2.1, Pharsight Corp.). The relationship of individual day 1 and steady-state Cmax and AUC values versus taselisib (GDC-0032) dose was evaluated with a power law model (C_{max} or AUC = a (Dose)^{bpower}) with 95% confidence interval of slope to the PK relationship between dose and taselisib exposure (C_{max} or AUC).

FDG-PET Imaging

To assess the effects of taselisib on tumor metabolism or as a marker of response to therapy, FDG–PET scans were obtained at baseline and during the last week of cycle 1 if at least one PET-assessable lesion was observed at baseline. Any significant changes in tumor FDG uptake required a repeat FDG–PET during cycle 2. For PET evaluation, up to 5 target lesions with a target to background uptake level greater than or equal to 2 were selected in the screening scan. Target lesions were to measure at least 15 mm in longest diameter (LD) on CT or MRI. In the case there were not 15 mm–diameter FDG–avid lesions, lesions of at least 10 mm in LD meeting RECIST 1.0 criteria were selected. An FDG–PET PMR was defined as a decrease of ≥ 20% in the average percentage change in the maximum standardized uptake value (SUV_{max}) of the target lesion.
RPPA Analysis of Tumor Biopsies

To assess PD effects on tumor and whether inhibition of PI3K with taselisib resulted in changes in pathway markers, pre- and posttreatment paired tumor biopsies were obtained at baseline and during cycle 1 from patients who provided consent for tissue biopsy. Tumor samples were assessed for decreased phosphorylation on downstream analytes, such as proline-rich Akt substrate 40 (pPRAS40), phosphorylated ERK (pERK), and phosphorylated ribosomal protein S6 (pRPS6), using RPPA (Theranostics) as previously described (35).

Tumor Assessments

Taselisib activity was evaluated by tumor CT assessments every 8 weeks, with confirmation of objective response ≥ 4 weeks after initial documentation (per RECIST v1.1).

Determination of PIK3CA Mutation Status

A patient was determined to harbor a PIK3CA-mutant tumor if a positive mutation result was obtained from either tissue or plasma.

Assessment of somatic mutations from tissue. PIK3CA mutation hot-spot status was assessed centrally using a PCR-based platform from DNA extracted from paraffin-embedded formalin-fixed tissue using PCR-based platforms as described previously (36). PIK3CA hotspot coverage included C420R, E542K, E545A/G/K, and H1047L/R/Y. Samples were subsequently molecularly profiled using an internally developed 120 somatic hotspot mutation test (MUT-MAP) that detected somatic mutations in AKT1, BRAF, EGFR, GFR3, FLT3, HRAS, KIT, MET, NRAS, and PIK3CA, as described previously (37). In addition to the central assessment of the eight PIK3CA hotspot mutations, the MUT-MAP somatic mutation test detected an additional nine mutations: R88Q, N345K, E545D, Q546R/K/L, M1043I, and G1049R.

Assessment of somatic mutations from plasma. ctDNA analysis of somatic mutations was determined centrally using the Sysmex Inostics Oncobeam Panel 1, which detects hotspot mutations in AKTI, BRAF, KRAS, NRAS, and PIK3CA. PIK3CA hotspot coverage included E542K, E545G/K, Q546K, M1043I, and H1047L/R/Y.

Determination of PTEN status. PTEN status was centrally determined using the Ventana Benchmark XT instrument with standard immunohistochemistry techniques and employing an anti-PTEN antibody (clone 138G6; Cell Signaling Technology). Samples were scored using an H-score methodology using the following equation: H-score = (% x 0) + (% x 1+) + (% x 2+) + (% x 3+) + (% x 4+), where 3+ is the staining intensity of surrounding normal tissue. A PTEN-null tumor was defined as H-score of 0, a PTEN-low tumor was defined as H-score between 1 and 100, and a PTEN-normal tumor was defined as H-score greater than 100.

Statistical Methods

The sample size for this study was based on the dose-escalation rules described in the study design section and was not based on explicit power or type I error considerations. Safety analyses included all patients who received any amount of taselisib. All AEs occurring on or after treatment on day 1 were summarized by mapped term, appropriate thesaurus levels, and NCI CTCAE v4.0 toxicity grade.

Disclosure of Potential Conflicts of Interest

D. Juric is a consultant/advisory board member for Eisai, EMD Serono, and Novartis. I. Krop reports receiving a commercial research grant from Genentech and is a consultant/advisory board member for the same. T.R. Wilson has ownership interest (including patents) in Roche. L. Salphati has ownership interest (including patents) in Roche/Genentech. J. Baselga is a consultant/advisory board member for Roche/Genentech, Seragon, Novartis, Eli Lilly, Aura Biosciences, Northern Biologics, ApoGen, Juno Therapeutics, and Tango; he is also a member of the Board of Directors of Foghorn Therapeutics, Infinity Pharmaceuticals, Grail, and Varian. No potential conflicts of interest were disclosed by the other authors.

One of the Editors-in-Chief is an author on this article. In keeping with the AACR’s editorial policy, the peer review of this submission was managed by a senior member of Cancer Discovery’s editorial team; a member of the AACR Publications Committee rendered the final decision concerning acceptability.

Authors’ Contributions

Conception and design: D. Juric, I. Krop, D. Sampath, R.S. Lin, H. Parmar, J.Y. Hsu, D.D. Von Hoff, J. Baselga
Development of methodology: T.R. Wilson, J.A. Ware, D. Sampath, R.S. Lin, H. Parmar, J.Y. Hsu, J. Baselga
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): D. Juric, I. Krop, R.K. Ramanathan, T.R. Wilson, D. Sampath, J.Y. Hsu, D.D. Von Hoff, J. Baselga
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): D. Juric, T.R. Wilson, J.A. Ware, S.M. Sanabria Bohorquez, D. Sampath, L. Salphati, R.S. Lin, H. Jin, H. Parmar, J.Y. Hsu, J. Baselga
Writing, review, and/or revision of the manuscript: D. Juric, I. Krop, R.K. Ramanathan, T.R. Wilson, J.A. Ware, D. Sampath, L. Salphati, R.S. Lin, H. Jin, H. Parmar, J.Y. Hsu, D.D. Von Hoff, J. Baselga
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): D. Juric, H.M. Savage, R.S. Lin

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Correction: Phase I Dose-Escalation Study of Taselisib, an Oral PI3K Inhibitor, in Patients with Advanced Solid Tumors

In the original version of this article (1), the stated disclosure of José Baselga is incorrect. The error has been corrected in the latest online HTML and PDF versions of the article. The authors regret this error.

REFERENCE


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