A phase I/II study evaluating GDC-0077 + palbociclib (palbo) + fulvestrant in patients (pts) with PIK3CA-mutant (mut), hormone receptor-positive/HER2-negative metastatic breast cancer (HR+/HER2- mBC)

PD1-02

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Methods

Safety (NCI-CTCAE v4), pharmacokinetics (PK) and pharmacodynamics (PD) were assessed via RECIST v1.1 of inavolisib 9 mg oral daily + palbociclib 125 mg/21/28 days = fulvestrant 600 mg intramuscularly on Day 1 and Day 15 of Cycle 1/2/3/4 cycles, were assessed in Arms E and F, until intolerance or disease progression (Figure 1).

This was a parallel, non-randomized analysis.

In Arm F, pts were obese and/or pre-diabetic (body mass index ≥25 kg/m2 and/or hemoglobin A1c ≥5.7%).

Pts also received metformin ≤2000 mg daily, starting at 500 mg at Cycle 1, prior to initiating inavolisib at Cycle 1, Day 15 instead of Day 1 in Arm E (Figure 2).

Results

Patients

The time data cut-off for the analysis was July 24, 2020. 30 pts were enrolled: 20 in Arm E and 10 in Arm F. Enrollment was ongoing in Arm E. Baseline characteristics are shown in Table 1.

Sixteen pts (80%) discontinued treatment: 14 due to radiographic disease progression (5 in Arm E, 9 in Arm F); one due to an adverse event (AE; treatment-related Grade 2 pneumonitis in Arm F) and one withdrew (Arm F).

Table 1: Pt characteristics and treatment exposure

| Arm | No. of pts | Median age (range) | Males | ECOG PS 0–1 | Prior AI‡ | Prior CDK4/6 inhibitor | Prior fulvestrant | Median cumulative palbocilib dose intensity | Median inavolisib treatment duration, months (range) | Median cumulative palbocilib dose | Median body mass index, kg/m² (range) | Prior CDK inhibitor | Prior PI3K or CDK4/6 inhibitor | Median cumulative inavolisib dose intensity | Median cumulative inavolisib dose intensity | MedDRA adverse events during treatment | AE during treatment |
|-----|------------|--------------------|-------|-------------|-----------|------------------------|-----------------|-------------------------------------------|---------------------------------|------------------------------------------|-------------------------------------------|-------------------------------|---------------------|-------------------|-----------------------------------|-----------------------------------|----------------------------------|----------------------------------|
| E  | 20         | 65 (25–81)         | 12    | 0–1         | 12 (75%)  | 10 (63%)               | 3 (15%)         | 86%                                       | 6.8 (1.1–17.7)                  | 15 (0–42)                              | 6 (23–37)                               | 25 (19.2–38.0) | 3 (15%)           | 3 (15%)                   | 60%                               | AEs: Nausea, Diarrhea, Fatigue, Alopecia, Hyperglycemia | AE: Nausea, Diarrhea, Fatigue, Alopecia, Hyperglycemia |
| F  | 10         | 65 (37–79)         | 6     | 0–1         | 10 (100%) | 12 (100%)              | 12 (100%)       | 95%                                       | 6.3 (1.2–15.3)                  | 11 (50–100)                            | 2 (20–100)                              | 33 (28.4–42.1) | 12 (120%)         | 12 (120%)               | 69%                               | AEs: Nausea, Diarrhea, Fatigue, Alopecia, Hyperglycemia | AE: Nausea, Diarrhea, Fatigue, Alopecia, Hyperglycemia |

Pharmacodynamics

There were limited data from cDNA analysis of PIK3CA/akt allele frequency; however, decreases of PIK3CA/akt frequency were observed over time in some patients experiencing stable disease or a PR (Figure 4).

Pharmacokinetics

The PK of inavolisib in combination with palbociclib + fulvestrant was similar to that of single-agent inavolisib.

There were no drug-drug interactions between inavolisib and concomitant therapies (palbociclib and fulvestrant) and [modest] administered PKs of inavolisib.

Conflict of interest

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References

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Background

Inavolisib (GDC-0077) is a PI3Kα-selective inhibitor and must PIK3CA degrader that demonstrates antitumor activity in pts with HR+/HER2-, PIK3CA-mut SC-64646, as a single agent or in combination therapy.1,2

A Phase I/II study of inavolisib alone and combined with endocrine therapy + palbociclib is ongoing (NCT03998972). The current data from this study, assessing pts with HR+/HER2-, PIK3CA-mut BC treated with inavolisib + palbociclib + fulvestrant.

Methods

Safety (NCI-CTCAE v4), pharmacokinetics (PK), and pharmacodynamics (PD) were evaluated via RECIST v1.1 of inavolisib 9 mg oral daily + palbociclib 125 mg/21/28 days + fulvestrant 600 mg intramuscularly on Day 1 and Day 15 of Cycle 1/2/3/4 cycles, were assessed in Arms E and F, until intolerance or disease progression (Figure 1).

This was a parallel, non-randomized analysis.

In Arm F, pts were obese and/or pre-diabetic (body mass index ≥25 kg/m2 and/or hemoglobin A1c ≥5.7%).

Pts also received metformin ≤2000 mg daily, starting at 500 mg at Cycle 1, prior to initiating inavolisib at Cycle 1, Day 15 instead of Day 1 as in Arm E (Figure 2).

Safety

Treatment-related (adverse events that equal to or exceeded grade 3) in 24 pts in either arm, and corresponding treatment-related grade 3 to 4 AEs

| Pt | No. of pts | Nausea | Diarrhea | Dyspepsia | Fatigue | Alopecia | Hyperglycemia | Stomatitis | Total number of pts with at least one AE (%)
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<tbody>
<tr>
<td>E</td>
<td>20</td>
<td>5 (25%)</td>
<td>9 (45%)</td>
<td>0</td>
<td>5 (25%)</td>
<td>4 (20%)</td>
<td>12 (60%)</td>
<td>5 (25%)</td>
<td>9 (25%)</td>
</tr>
<tr>
<td>F</td>
<td>10</td>
<td>0</td>
<td>1 (5%)</td>
<td>0</td>
<td>3 (19%)</td>
<td>0</td>
<td>11 (69%)</td>
<td>1 (5%)</td>
<td>8 (50%)</td>
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Grade 2 panniculitis in Arm F); and one withdrew (Arm F).

AEs during treatment

AEs: Nausea, Diarrhea, Fatigue, Alopecia, Hyperglycemia

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AE: Nausea, Diarrhea, Fatigue, Alopecia, Hyperglycemia

Figure 4: cDNA PIK3CA/akt for Arm E (n = 4) and F (n = 10) between C1D1 and C4D1

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This phase I/II study demonstrated a manageable safety profile when combining inavolisib at its single-agent recommended phase II dose of 9 mg with palbociclib + fulvestrant at standard doses, with no unexpected safety signals with similar PK in inavolisib alone. In obese and/or pre-diabetic pts enrolled in Arm F, hyperglycemia was frequent despite initiating metformin prior to baseline.

Encouraging preliminary antitumor activity with a response rate of 40% was observed in Arm E (13% in Arm F). There were limited data for modulation of PIK3CA/akt allele frequency.

Refer to Oliveira et al. (SABCS poster PS11-11) for a summary of targeted safety in inavolisib alone in combination with endocrine therapy + palbociclib in this phase I/II study.

A phase III study of inavolisib + fulvestrant + plus placebo in pts with HR+ mBC, PIK3CA-mut has been ongoing (NCT04191480).

Conclusion

This phase I/II study demonstrated a manageable safety profile when combining inavolisib at its single-agent recommended phase II dose of 9 mg with palbociclib + fulvestrant at standard doses, with no unexpected safety signals with similar PK in inavolisib alone. In obese and/or pre-diabetic pts enrolled in Arm F, hyperglycemia was frequent despite initiating metformin prior to baseline.

Overall, among patients with measurable disease:

Six of 15 pts (40%) had a partial response (PR) in Arm E; 2/13 pts (15%) had a PR in Arm F (both received prior fulvestrant).

Clinical benefit (defined as stable disease for 24 weeks, PR, or complete response) was 58% (2/13/16 pts: 12 in Arm F, none in Arm E).

One pt in Arm F with evaluable-only disease had a CR.