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# Ipatasertib combined with non-taxane chemotherapy for patients with previously treated advanced triple-negative breast cancer: the PATHFINDER phase IIa trial

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## BACKGROUND

- The PI3K/AKT signaling pathway plays a crucial part in carcinogenesis, promoting cellular metabolism, proliferation, and invasion[1] . About one third of all triple-negative breast cancers (TNBC) harbor ***PIK3CA/AKT1/PTEN*** alterations, representing a novel therapeutic target[2-4].
- Ipatasertib (GDC-0068) [IPA] is a potent and selective pan-AKT inhibitor that has shown, alone or combined, promise for treating advanced solid tumors[5-6].
- The PATHFINDER trial evaluated the safety, tolerability, and preliminary efficacy of ipatasertib in combination with non-taxane chemotherapy (capecitabine, eribulin, and carboplatin plus gemcitabine) in taxane-pretreated advanced TNBC patients (pts).

## STUDY DESIGN

PATHFINDER is a multicenter, open-label, three-arm, non-comparative, phase II trial **with a safety run-in stage.**

### KEY SELECTION CRITERIA

- Women aged ≥18 years with unresectable locally advanced or metastatic TNBC.
- Progression after 1-2 prior chemotherapy regimens for advanced disease*.
- Prior therapy must have included a taxane in any setting.
- Eligible for capecitabine, eribulin, or carboplatin plus gemcitabine.
- Measurable or evaluable disease as per RECIST v.1.1.
- Pts with treated and stable brain metastases were eligible.
- ECOG performance status 0-1.
- No prior treatments with PI3K, mTOR, and/or AKT inhibitors were allowed.

N=22 → ARM A: **Ipatasertib + Capecitabine** — 3 pts safety run-in phase, 19 pts phase II

N=25 → ARM B: **Ipatasertib + Eribulin** — 3 pts safety run-in phase, 22 pts phase II

N=7 → ARM C: **Ipatasertib + Carboplatin + Gemcitabine** — 7 pts safety run-in phase

### PRIMARY ENDPOINT

- Incidence, nature, and severity of AEs graded per the NCI-CTCAE v.5.0.

### SECONDARY ENDPOINTS

- PFS, TTR, ORR, DoR, OS, and best percentage of change in target tumor lesions determined through use of RECIST v.1.1.

### EXPLORATORY ENDPOINTS

- Clinical outcome according to the *PIK3CA/AKT1/PTEN* -altered status.
- Predictive and/or prognostic factors associated to ipatasertib-containing treatments.

*Earlier (neo)adjuvant therapy was considered as a prior regimen if DFI≤12 months after completion of chemotherapy.

### ARM A

Oral IPA 400 mg once a day on Days 1-14 plus oral capecitabine 1000 mg/m² twice a day for 14 days (followed by a 7-day rest period), every 21-day cycle.

### ARM B

Oral IPA 400 mg once a day on Days 1-14 plus intravenous eribulin 1.23 mg/m² on Days 1 and 8, every 21-day cycle.

### ARM C

Oral IPA 400 mg once a day on Days 1-14 plus intravenous carboplatin AUC5 on Day 1 and gemcitabine 1000 mg/m² on Days 1 and 8, every 21-day cycle.

## STATISTICAL CONSIDERATIONS

- Statistical analysis was exploratory with no hypothesis testing.
- Expected sample size provided the following precisions:
  - 95% Clopper-Pearson confidence interval (CI) of 81.5% to 100.0%, assuming an observed adverse events (AEs) incidence of 100.0%.
  - 95% Clopper-Pearson confidence interval of 26.0% to 74.0%, assuming an observed AEs incidence of 50.0%.
- Based on a previous trial[6], an estimation of 100.0% incidence of all grades and 50.0% grade ≥3 AEs was assumed.

**Abbreviations: AEs:** Adverse Events; **AESIs:** Adverse Events Of Special Interest; **AKT:** A serine/threonine protein kinase; **ALT:** Alanine Aminotransferase; **AUC:** Area Under the Curve; **CBR:** Clinical Benefit Rate; **CI:** Confidence Interval; **CR:** Complete Response; **DFI:** Disease-Free Interval; **DoR:** Duration Of Response; **ECOG:** Eastern Cooperative Oncology Group; **IPA:** Ipatasertib; **KM Est:** Kaplan-Meier Estimand; **mTOR:** Mammalian Target of Rapamycin; **n:** number of patients; **NCI-CTCAE:** National Cancer Institute-Common Terminology Criteria for Adverse Events; **NE:** Not Evaluable; **ORR:** Objective Response Rate; **OS:** Overall Survival; **PD:** Progressive Disease; **PI3K:** Phosphoinositide 3-Kinase; **PFS:** Progression-Free Survival; **PR:** Partial Response; **PTEN:** Phosphatase and tensin homolog; **pts:** patients; **RECIST:** Response Evaluation Criteria in Solid Tumors; **SD:** Stable Disease; **TEAEs:** Treatment Emergent Adverse Events; **TNBC:** Triple-Negative Breast Cancer; **TTR:** Time To Response; **w:** weeks.

## RESULTS

- From 30th July 2020 to 11st November 2022, 54 patients were enrolled in the PATHFINDER study and allocated in arm A (N=22), arm B (N=25), and arm C (N=7).
- The safety run-in phase included 3 patients in arm A, 3 patients in arm B, and 7 patients in arm C.
- Total significant toxicities in arm C during the safety run-in stage led to premature interruption of this treatment arm.
- At data cut-off (November 11, 2023) all patients had discontinued treatment, with a median follow-up of 13.5 (range: 2.4-35.5), 11.2 (range: 0.2-36.9), and 9.2 (range: 1.0-35.6) months in arms A, B and C, respectively.

**Table 1**. Patients' demographic characteristics at baseline

| n (%) | Arm A (N=22) | Arm B (N=25) | Arm C (N=7) |
|---|---|---|---|
| **Age, median (range) years** | 54.5 (34.0; 79.0) | 55.0 (35.0; 79.0) | 59.0 (38.0; 68.0) |
| **ECOG performance status** | | | |
| **0** | 18 (81.8) | 17 (68.0) | 3 (42.8) |
| **1** | 4 (18.2) | 8 (32.0) | 4 (57.2) |
| **TNBC at initial diagnosis** | 20 (90.9) | 20 (80.0) | 7 (100.0) |
| **Prior chemotherapy in the (neo)adjuvant setting** | | | |
| **Yes** | 15 (68.2) | 19 (76.0) | 6 (85.7) |
| **No** | 7 (31.8) | 6 (24.0) | 1 (14.3) |
| **Prior chemotherapy regimens for advanced disease** | | | |
| **0*** | 5 (22.7) | 8 (32.0) | 3 (42.8) |
| **1** | 15 (68.2) | 9 (36.0) | 2 (28.6) |
| **2** | 2 (9.1) | 8 (32.0) | 2 (28.6) |
| **Visceral involvement** | | | |
| **Yes** | 17 (77.3) | 22 (88.0) | 7 (100.0) |
| **No** | 5 (22.7) | 11 (44.0) | 1 (14.3) |
| **Number of metastatic sites** | | | |
| **<3** | 14 (63.6) | 19 (76.0) | 6 (85.7) |
| **≥3** | 8 (36.4) | 6 (24.0) | 1 (14.3) |
| **Metastatic sites** | | | |
| **Lymph node** | 11 (50.0) | 11 (44.0) | 2 (28.6) |
| **Lung** | 11 (50.0) | 7 (28.0) | 5 (71.4) |
| **Bone** | 9 (40.9) | 15 (60.0) | 5 (71.4) |
| **Liver** | 7 (31.8) | 7 (28.0) | 0 (0.0) |

* Earlier systemic treatment in the curative setting was considered as one line of therapy if the development of unresectable locally advanced or metastatic disease occurred within a 12-month period after completion of treatment.

- Incidence of grade ≥3 TEAEs by maximum severity was 27.3% in arm A, 68.0% in arm B, and 100.0% in arm C:
  - Arm A: neutropenia (4.5%).
  - Arm B: neutropenia (32.0%), rash (16.0%), stomatitis (8.0%), and diarrhea (4.0%).
  - Arm C: thrombocytopenia (85.7%), neutropenia (71.3%), anemia (57.2%), febrile neutropenia (28.6%), and nausea (28.6%).

**Table 2**. Overview safety summary in each arm

| n (%) | Arm A (N=22) | Arm B (N=25) | Arm C (N=7) |
|---|---|---|---|
| **AEs** | 22 (100.0) | 24 (96.0) | 7 (100.0) |
| **TEAEs** | 21 (95.5) | 24 (96.0) | 7 (100.0) |
| Related | 18 (81.8) | 22 (88.0) | 7 (100.0) |
| Related to ipatasertib | 7 (31.8) | 18 (72.0) | 4 (57.2) |
| Related to both medications | 12 (54.5) | 11 (44.0) | 7 (100.0) |
| **Grade ≥3 TEAEs** | 6 (27.3) | 17 (68.0) | 7 (100.0) |
| Related | 2 (9.1) | 14 (56.0) | 7 (100.0) |
| Related to ipatasertib | 1 (4.5) | 6 (24.0) | 2 (28.6) |
| Related to both medications | 1 (4.5) | 2 (8.0) | 6 (85.7) |
| **AESIs*** | 1 (4.5) | 6 (24.0) | 2 (28.6) |
| Related | 1 (4.5) | 5 (20.0) | 2 (28.6) |
| Related to ipatasertib | 0 (0.0) | 5 (20.0) | 0 (0.0) |
| Related to both medications | 1 (4.5) | 0 (0.0) | 2 (28.6) |
| **Serious TEAEs** | 2 (9.1) | 9 (36.0) | 4 (57.2) |
| Related | 1 (4.5) | 5 (20.0) | 4 (57.2) |
| Related to ipatasertib | 0 (0.0) | 1 (4.0) | 0 (0.0) |
| Related to both medications | 1 (4.5) | 1 (4.0) | 4 (42.8) |
| **TEAEs associated to drug discontinuation** | 1 (4.5) | 2 (8.0) | 4 (42.8) |
| Related | 0 (0.0) | 2 (8.0) | 4 (42.8) |
| Related to ipatasertib | 0 (0.0) | 1 (4.0) | 0 (0.0) |
| Related to both medications | 0 (0.0) | 0 (0.0) | 2 (28.6) |
| **TEAEs associated with an outcome of death** | 0 (0.0) | 2 (8.0) | 0 (0.0) |
| **Unrelated** | 0 (0.0) | 2** (8.0) | 0 (0.0) |

* Pneumonia due to COVID-19 and hyperacute ischemic stroke.
** AESIs included transmission of an infectious agent by the study drug, drug-induced liver injury, G≥3 hyperglycemia, G≥3 diarrhea, G≥3 rash, G≥2 colitis/enterocolitis, and G≥2 pneumonitis.

**Figure 1.** Most common (≥15% of patients in any subgroup) any grade TEAEs by maximum severity

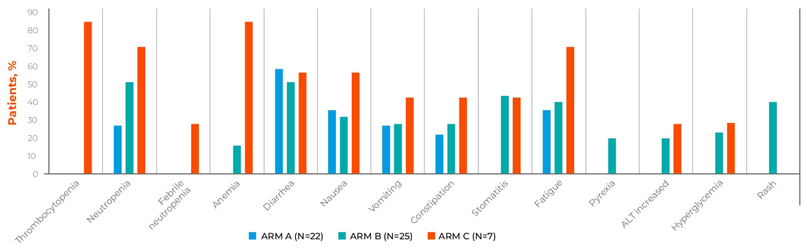



**Figure 2.** Progression-free survival

| Arm | Events/Total | Median (95% CI) | Time-Point | KM Est (95% CI) |
|---|---|---|---|---|
| Arm A | 19/22 (86.4%) | 2.7 (1.5-4.1) | 12 months<br>24 months | 7.2 (0.6-25.7%)<br>7.2 (0.6-25.7%) |
| Arm B | 20/25 (80.0%) | 3.8 (1.5-9.6) | 12 months<br>24 months | 18.2 (5.7-36.3%)<br>9.1 (0.9-29.9%) |
| Arm C | 6/7 (85.7%) | 5.3 (1.4-34.2) | 12 months<br>24 months | 16.7 (0.8-51.7%)<br>16.7 (0.8-51.7%) |

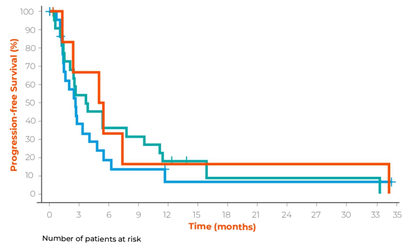



**Figure 3**. Overall survival

| Arm | Events/Total | Median (95% CI) | Time-Point | KM Est (95% CI) |
|---|---|---|---|---|
| Arm A | 15/22 (68.2%) | 15.5 (11.8-19.3) | 12 months<br>24 months | 70.5 (45.7-85.6%)<br>13.1 (2.2-33.9%) |
| Arm B | 17/25 (68.0%) | 11.5 (8.8-25.1) | 12 months<br>24 months | 43.6 (23.3-62.2%)<br>33.6 (15.3-53.1%) |
| Arm C | 4/7 (57.1%) | 12.1 (2.8-NE) | 12 months<br>24 months | 50.0 (11.1-80.4%)<br>33.3 (4.6-67.6%) |

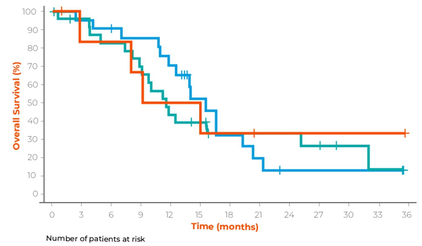



**Table 3**. Best tumor response according to RECIST v.1.1

| Response, n (%) | Arm A (N=22) | Arm B (N=25) | Arm C (N=7) |
|---|---|---|---|
| **ORR* [95% CI]** | 2 (9.1) [1.1; 29.0] | 9 (36.0) [18.0; 57.5] | 2 (28.6) [3.7;71.0] |
| **CR** | 1 (4.5) | 0 (0.0) | 0 (0.0) |
| **PR** | 1 (4.5) | 9 (36.0) | 2 (28.6) |
| **SD≥24w** | 3 (13.6) | 4 (16.0) | 2 (28.6) |
| **SD<24w** | 9 (40.9) | 4 (16.0) | 1 (14.3) |
| **PD** | 8 (36.4) | 3 (12.0) | 1 (14.3) |
| **NE** | 0 (0.0) | 5 (20.0) | 1 (14.3) |
| **CBR* [95% CI]** | 5 (22.6) [7.8 ; 45.4] | 13 (52.0) [31.3 ; 72.2] | 4 (57.2) [8.4 ; 90.1] |

* Unconfirmed

## CONCLUSIONS

- **Combining ipatasertib with capecitabine or eribulin demonstrated an acceptable and manageable safety profile.**
- **Adding ipatasertib to carboplatin plus gemcitabine was considered not tolerable.**
- **Compared with historical controls[7,8], the addition of ipatasertib to eribulin seems to improve PFS in this biomarker unselected population.**
- **The PI3K mutational status in arms A and B is currently under examination to evaluate its potential as a predictor of efficacy.**

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