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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, an estimation of 100.0% incidence of all grades and 50.0% grade ≥3 AEs was assumed[6].

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

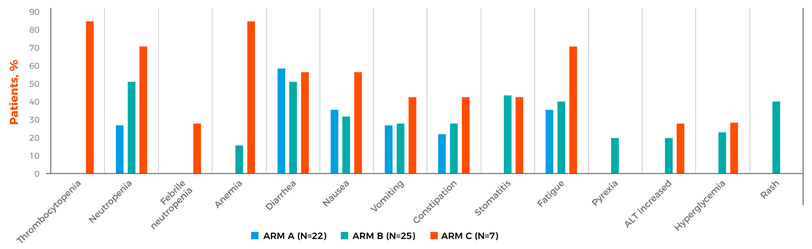
- From 30th July 2020 to 11st November 2022, 54 patients were enrolled in the PATHFINDER study and allocated in arm A (N=22), arm B (N=25), and arm C (N=7).
- The safety run-in phase included 3 patients in arm A, 3 patients in arm B, and 7 patients in arm C.
- Total significant toxicities in arm C during 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.

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



- 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%).

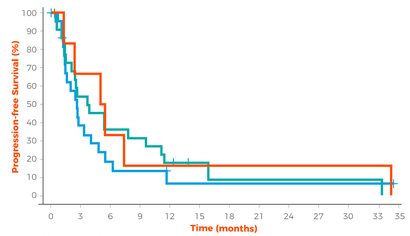
Table 2. Overview safety summary in each arm

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 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	7.2 (0.6-25.7%)
			24 months	7.2 (0.6-25.7%)
Arm B	20/25 (80.0%)	3.8 (1.5-9.6)	12 months	18.2 (5.7-36.3%)
			24 months	9.1 (0.9-29.8%)
Arm C	6/7 (85.7%)	5.3 (1.4-34.2)	12 months	16.7 (0.8-51.7%)
			24 months	16.7 (0.8-51.7%)

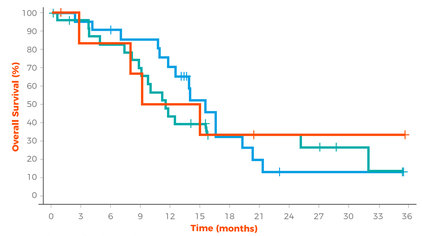


Number of patients at risk

Arm A	22	8	4	3	1	1	1	1	1	1	1	1
Arm B	25	12	8	7	4	2	1	1	1	1	1	1
Arm C	7	4	2	1	1	1	1	1	1	1	1	1

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	70.5 (45.7-85.6%)
			24 months	13.1 (2.2-33.9%)
Arm B	17/25 (68.0%)	11.5 (8.8-25.1)	12 months	43.6 (23.3-62.2%)
			24 months	33.6 (15.3-53.1%)
Arm C	4/7 (57.1%)	12.1 (2.8-NE)	12 months	50.0 (11.1-80.4%)
			24 months	33.3 (4.6-67.6%)



Number of patients at risk

Arm A	22	20	18	17	14	8	5	3	1	1	1	1	0
Arm B	25	22	19	16	10	8	5	5	5	4	2	1	1
Arm C	7	5	5	4	3	2	2	1	1	1	1	1	0

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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