A phase I/Ib study evaluating GDC-0077 plus fulvestrant in patients with *PIK3CA*-mutant, hormone receptor-positive/HER2-negative breast cancer

Abstract # 10349

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Disclosures

Nature	Company
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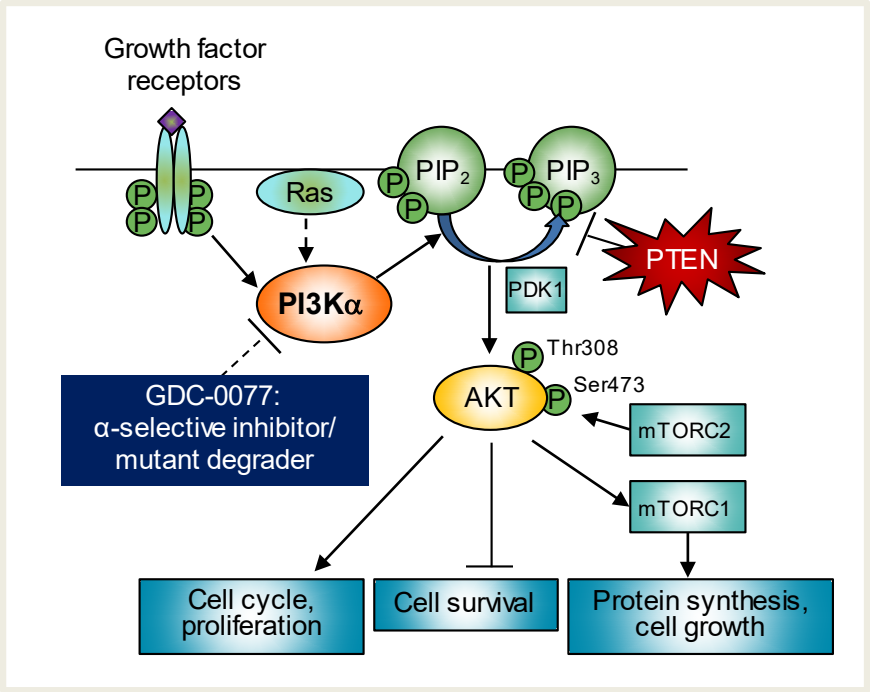
GDC-0077 is an alpha isoform-selective, mutant degrading inhibitor of PI3K

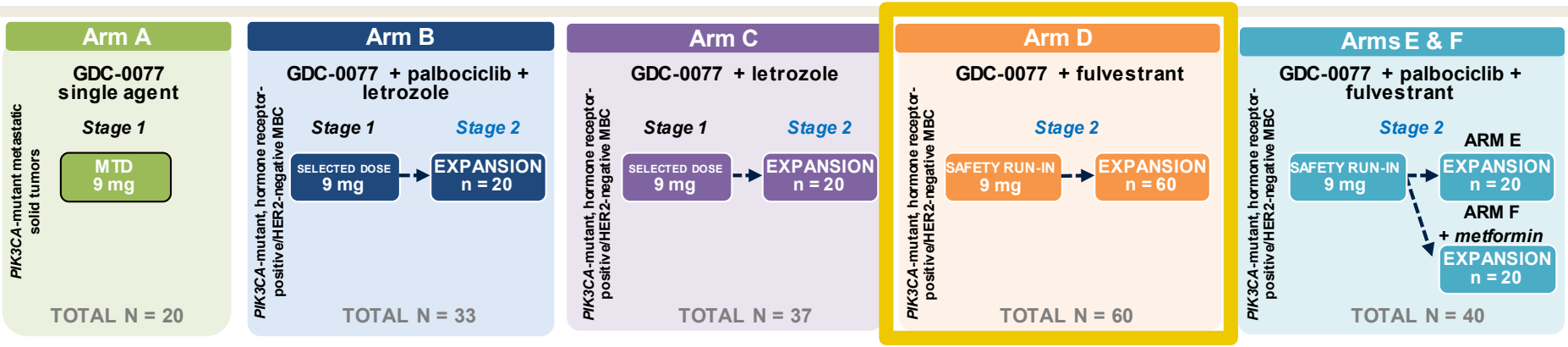
- *PIK3CA* encodes the PI3K p110α subunit; dysregulating mutations are widely seen in breast cancer and other solid tumors and are associated with oncogenesis
- **GDC-0077 is a potent, selective inhibitor of p110α, the catalytic subunit of PI3Kα, and a specific degrader of mutant p110α**
- GDC-0077 demonstrates antitumor activity in *PIK3CA*-mutant breast cancer xenograft models as a single agent and in combination with antiestrogen therapy[1]



AKT, protein kinase B; mTORC1, mammalian target of rapamycin complex 1; mTORC2, mammalian target of rapamycin complex 2; PDK1, phosphoinositide-dependent kinase-1; PI3K, phosphatidylinositol 3-kinase; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; PIP_2, phosphatidylinositol-3,4-bisphosphate; PIP_3, phosphatidylinositol-3,4,5-trisphosphate; PTEN, phosphatase and tensin homolog; RTK, receptor tyrosine kinase; Ser473, serine473; Thr308, threonine 308.

1. Edgar K, *et al. Cancer Res* 2017; **77:** Abstract 156 (and associated poster presentation).

A phase I/Ib study evaluating GDC-0077 alone and combined with endocrine therapies plus palbociclib in patients with *PIK3CA*-mutant, hormone receptor-positive/HER2-negative metastatic breast cancer (NCT03006172)



- **Presented data are from the food-effect portion of GDC-0077 plus fulvestrant** in 20 postmenopausal patients
  - GDC-0077 9 mg oral once daily plus intramuscular fulvestrant 500 mg on Day 1 (+ Day 15 of Cycle 1) of 28-day cycles until intolerable toxicity or disease progression
- **Endpoints:** Safety (NCI-CTCAE v4); PK, including food-effect assessment on the PK of GDC-0077; preliminary antitumor activity (RECIST v1.1); signaling and PD biomarkers using ctDNA
- **Baseline characteristics:** Median age 54.5 years (range: 31–85); 17 patients (85%) with ECOG 0; 7 patients (35%) with BMI ≥ 30 kg/m^2 and/or HbA1c* ≥ 5.7%; 15 patients (75%) with ≥ 2 prior metastatic therapeutic lines; 9 patients (45%) treated with 1 prior chemotherapy for metastatic breast cancer; 8 patients (40%) previously treated with fulvestrant; 18 patients (90%) with prior CDK4/6i

* Eligibility criteria required HbA1c < 7%. BMI, body mass index; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; HbA1c, glycated haemoglobin; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; MTD, maximum tolerated dose; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PD, pharmacodynamics; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; PK, pharmacokinetics; RECIST, Response Evaluation Criteria In Solid Tumors.

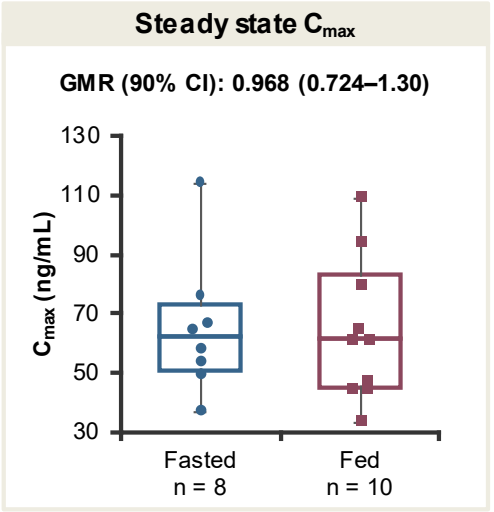
GDC-0077 demonstrated a manageable safety profile and no observable food effect on PK

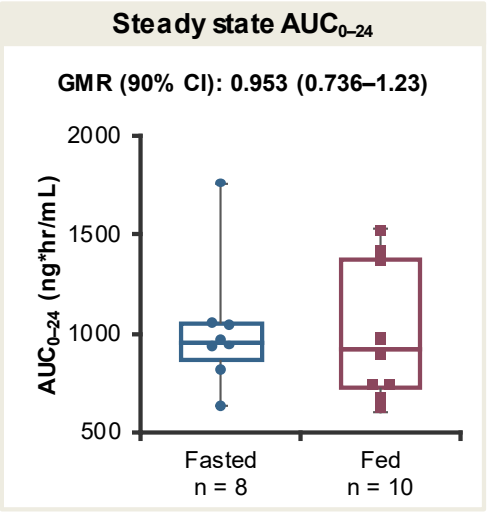
SAFETY

	N = 20
Discontinued treatment (all due to PD, none due to AEs)	17 (85%)
Median GDC-0077 duration, months (range)	5.9 (1.7–17.8)
Cumulative GDC-0077 dose intensity	98%
AEs leading to GDC-0077 dose reduction	3 (15%)
Common TRAEs (≥ 4 patients, 20%)	
Hyperglycemia	11 (55%)
Diarrhea	10 (50%)
Stomatitis*	9 (45%)
Nausea	8 (40%)
Decreased appetite	7 (35%)
Dysgeusia	4 (20%)
Fatigue	4 (20%)
Muscle spasms	4 (20%)
Grade ≥ 3 TRAEs	
Hyperglycemia	1 (5%)
Nausea	1 (5%)
Lymphopenia	1 (5%)
Hyperamylasemia	1 (5%)
Hyperlipasemia	1 (5%)

PK

- PK of GDC-0077 plus fulvestrant similar to single-agent PK
- Comparable GDC-0077 exposures (C_{max} and $AUC_{0–24}$) observed following administration in fasted or fed states (with a standard high-fat meal), after a single dose (data not shown) and at steady state

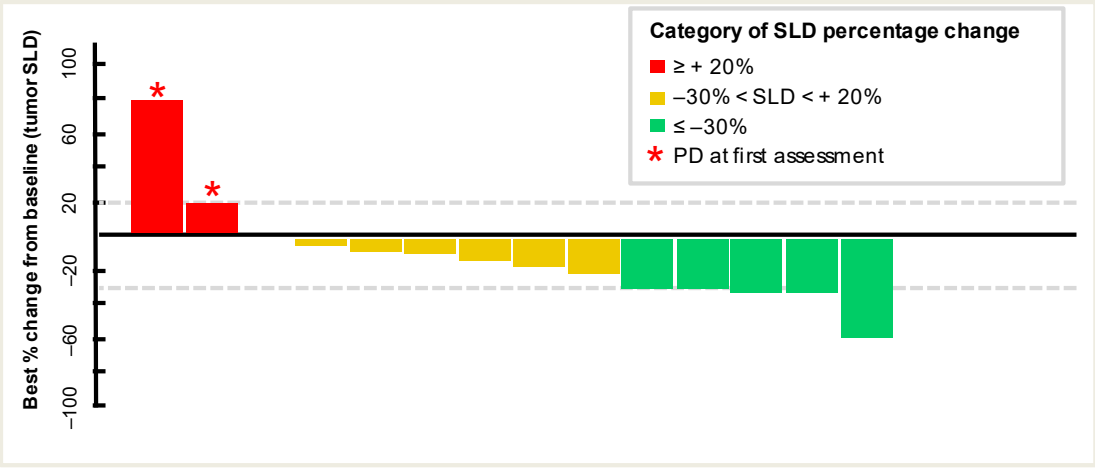




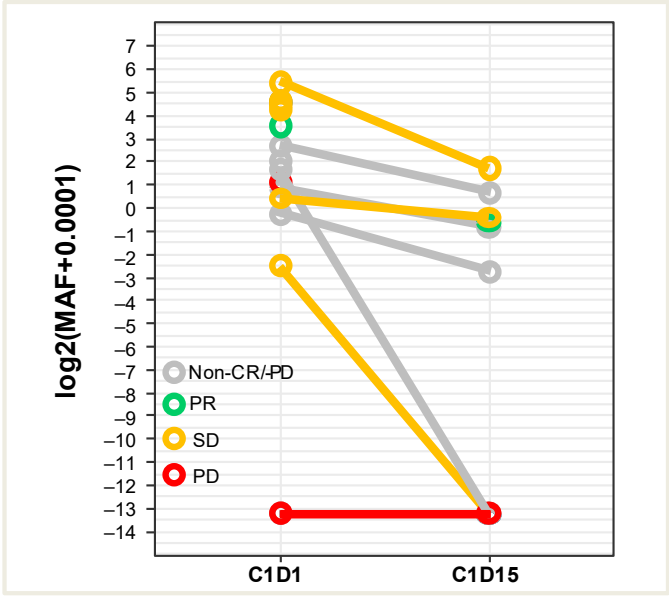
Data cutoff: July 19, 2019. * Grouped terms: stomatitis, mucosal inflammation, and mouth ulceration.
AEs, adverse events; $AUC_{0–24}$, area under the concentration–time curve at 0–24 hours; CI, confidence interval; C_{max}, maximum serum concentration; GMR, geometric mean ratio; PD, progressive disease; PK, pharmacokinetics; TRAEs, treatment-related adverse events.

GDC-0077 plus fulvestrant elicited antitumor activity and decreased *PIK3CA* mutant allele frequency in plasma

- Clinical benefit rate: 60% (12/20 patients)*
- PR in 5/14 patients with measurable disease (36%)
  - 2 patients received prior fulvestrant
  - 4 patients received prior CDK4/6i
  - Confirmed PR in 2 patients (14%)



- *PIK3CA* mutant allele frequency generally decreased as a result of study treatment in available paired ctDNA data



* Clinical benefit rate: SD for ≥ 24 weeks, PR, or CR.
C, cycle; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CR, complete response; ctDNA, circulating tumor DNA; D, day; MAF, mutant allele frequency; PD, progressive disease; PR, partial response; SD, stable disease; SLD, sum of longest diameters.

Conclusions

- GDC-0077 in combination with fulvestrant demonstrated a manageable safety profile, similar PK to GDC-0077 alone, preliminary antitumor activity, and PD modulation of *PIK3CA* mutant allele frequency in ctDNA
- The presence of food did not impact the rate or extent of GDC-0077 absorption significantly following single doses or at steady state
- This phase I/Ib study continues to enroll patients in the GDC-0077 plus fulvestrant and the GDC-0077 plus fulvestrant and palbociclib arms
  - A global phase III study of GDC-0077 plus fulvestrant and palbociclib is currently ongoing (NCT04191499)

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ctDNA, circulating tumor DNA; PD, pharmacodynamic; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; PK, pharmacokinetics.