

An open-label phase I study of GDC-0927 in postmenopausal women with locally advanced or metastatic estrogen receptor positive breast cancer

Sarat Chandarlapaty,¹ Maura N. Dickler,^{1,2} Jose Alejandro Perez Fidalgo,³ Rafael Villanueva-Vázquez,⁴ Jennifer Giltane,⁵ Mary Gates,⁵ Ching-Wei Chang,⁵ Sravanthi Cheeti,⁵ Jill Fredrickson,⁵ Xiaojing Wang,⁵ Ann Collier,⁵ Heather M. Moore,⁵ Ciara Metcalfe,⁵ Jennifer Lauchle,⁵ Eric W. Humke,^{5,6} Aditya Bardia⁷

Supplementary Materials

Supplementary Table. S1. Representatives of study participants.

Locally advanced or metastatic Estrogen receptor positive breast cancer (ER+/HER2-)	
Considerations related to:	
Sex	<p>The National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results Program (SEER) 5-year age-adjusted incidence rates (2015-2019) for breast cancer is 128.3 per 100,000 females and 1.3 per 100,000 males.</p> <p>HR+/HER2- is the most common subtype of breast cancer with an age-adjusted rate of 87.4 new cases per 100,000 women based on 2015-2019 cases.</p> <p>That means 68% of breast cancers in females are HR+/HER2-.</p>
Age	<p>Among females with HR+/HER2- breast cancer, the SEER (2015-2019) 5-year age-adjusted breast cancer incidence rate increases with each age group, peaking in the 70-74 year old age group (353.8 per 100,000), and then decreasing.</p>
Race/ ethnicity	<p>The SEER (2015-2019) 5-year age-adjusted HR+/HER2- breast cancer incidence rates per 100,000 females were 91.0 for Whites (including Hispanics) and 72.8 for Blacks (including Hispanics). Among non-Hispanic Asian/ Pacific Islander females, it was 71.6.</p>
Geography	<p>This study was conducted in USA and Spain.</p> <p>In USA in 2022, an estimated 287,850 new cases of invasive breast cancer were diagnosed in females, and 2,710 in males.</p> <p>In Spain in 2021, an estimated 33,375 new cases of breast cancer were diagnosed in females.</p>
Other considerations	<p>The SEER 5-year relative survival rates (2012-2018) for females with HR+/HER2- breast cancer were 95.1% for Whites (includes Hispanics), 94.3% for non-Hispanic Asians/ Pacific Islanders, and 88.0% for Blacks (includes Hispanics).</p>
Overall representativeness of this study	<p>This was small, phase 1 study of 42 females; race was known for 38 females. Among the 38, there were 33 (86.8%) White, 4 (10.5%) Black, and 1 (2.6%) Asian. This study was not powered to draw conclusions from representation of study participants.</p> <p>The median age in our study was 56 years. The median age for breast cancer diagnosis is 62 years (SEER).</p> <p>Male patients were not allowed to participate in this study.</p>
<p>Data source: https://seer.cancer.gov/statistics-network/explorer/application.html https://www.statista.com/statistics/779054/number-from-new-cases-from-cancer-by-kind-in-spain/</p>	

Supplementary Table S2. GDC-0927 pharmacokinetic parameters following single dose and at steady state (geometric mean, % CV).

	T_{max} (hr)*	C_{max} (ng/mL)	AUC_{0-24 hr} (hr·ng/mL)	AUC_∞ (hr·ng/mL)	t_{1/2} (hr)
Single dose					
600 mg (n=3)	3 (1–8)	58 (62)	648 (81)	1219 (67)	17 (16–23)
1000 mg (n=3)	1.5 (1–4)	129 (52)	1100 (26)	2267 (67)	17 (13–28)
1400 mg (n=9)	3 (1–10)	159 (38)	1413 (44)	3402 (44)	18 (9–37) [#]
Steady state					
600 mg (n=3)	1.5 (1.5–3)	88 (38)	1128 (37)	-	-
1000 mg (n=3)	3 (1.5–4)	158 (24)	1722 (54)	-	-
1400 mg (n=33)	3 (1–6)	166 (58)	1887 (55)	-	-

*Values reported as median (range). [#]n=5.

Supplementary Table S3. Immunohistochemistry and tumor *ESR1* mutation status of paired tissue samples ($n=9$). Histo (H)-scores, represented as a range of 0-300, are defined using the formula: (3 x percentage of positively stained tumor cell nuclei at strong intensity) + (2 x percentage of positively stained tumor cell nuclei at intermediate intensity) + (percentage of positively stained tumor cell nuclei at weak intensity). “NA” indicates no results available.

Patient #	Dose (mg)	Estrogen Receptor H-score		Progesterone Receptor H-score		Ki67 Percent positive		% <i>ESR1</i> mutant reads		
		At screening	On treatment	At Screening	On treatment	At screening	On treatment	At Screening	On treatment	Variant
1	600	190	90	20	113	NA	65	NA	NA	NA
2	1000	300	250	5	5	85	60	0	0	None
3	1400	225	200	0	0	2	5	0	0	None
4	1400	238	150	300	200	50	2	28	33	Y537S
5	1400	300	270	5	90	40	50	NA	NA	NA
6	1400	180	265	60	215	30	25	NA	NA	NA
7	1400	285	180	5	5	50	5	90	86	Y537N
8	1400	235	125	255	35	40	8	98/0	47/42	D538G/ Y537N
9	1400	285	70	0	0	25	13	0	0	None