Abstract 599

Real-World Use of PARP inhibitors in *BRCA*-Mutated Pancreatic Cancer: A Retrospective Analysis

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Objective.

- To assess the context of poly ADP-ribose polymerase inhibitors (PARPi) initiation in relation to use of platinum-based therapy and disease progression among metastatic pancreatic cancer (mPaC) patients with BRCA1/2 mutations in the real-world setting.

Conclusions

- More than half of mPaC patients with known BRCA1/2 mutation received a PARP inhibitor.
  - The context of PARPi use varied with respect to line of therapy and prior platinum history.
- These findings highlight the value of upfront genetic and molecular testing in mPaC where BRCA mutation status can inform treatment decision on platinum-based regimens and subsequent targeted therapies such as PARPi.

Limitations

- The database represented a convenience sample of patients with pancreatic cancer identified through a real-world registry of patient-initiated (e.g. via the Pancreatic Cancer Action Network Patient Central call center) and physician-initiated referrals; some data elements may be incomplete; and this sample may not be representative of all patients with pancreatic cancer in the US
- This is retrospective observational study of patients diagnosed with metastatic pancreatic cancer between 2012-2020 and may not reflect the most recent clinical practice on PARPi and platinum use
- Due to rarity in real world data of mPaC patients with BRCA mutation, this analyses was based on a moderate sample size.

Plain language summary

Why did we perform this research?
Patients with pancreatic cancer harboring a germline BRCA mutation showed improved response to platinum therapies. In addition, olaparib was approved for the maintenance treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) metastatic pancreatic adenocarcinoma, whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy. In light of these recent clinical findings, it is critical to understand the current real-world use of platinum-based therapies and PARPi among mPaC patients with BRCA mutation.

How did we perform this research?
Patients with metastatic pancreatic cancer and BRCA1/2 mutations were identified through the Perthera Know Your Tumor Real World Registry. Patients' characteristics and initiation of PARPi in relation to platinum exposure and disease progression were retrospectively assessed.

What were the findings of this research and what are the implications?
More than half of the patients with metastatic pancreatic cancer and BRCA1/2 mutation started a PARPi. The majority of patients with a BRCA1/2 mutation were treated with platinum-based therapy without disease progression but some switched to a PARPi after progression on platinums. These results highlight the importance of upfront BRCA testing which affects subsequent response and treatment decision regarding platinum and PARPi.

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Introduction

- BRCA1 or BRCA2 mutations can be found in approximately 4 to 8% of patients diagnosed with pancreatic adenocarcinoma[1,2,3].
- mPaC patients with a germline mutation in BRCA1/2 showed improved clinical outcomes when treated with platinum-based chemotherapies[4-5].
- The POLO trial[3] demonstrated clinical benefit of a PARPi (olaparib) in mPaC patients who had a germline BRCA mutation, and had received at least 16 weeks of first-line platinum-based chemotherapy without disease progression.
- In this analysis, we assessed PARPi initiation among real-world mPaC patients with germline or somatic BRCA1/2 mutations, in relation to their use of platinum-based therapy and disease progression.

Results

- PARPi use was documented in 60% (33 out of 55) of mPaC patients with BRCA1/2 mutation in any treatment setting. Within this cohort, 21 patients received a single agent PARPi in a real world setting (**Figure 2**), whereas the other 12 patients received PARPi through clinical trials or in combination of other agents.
- Among patients with BRCA1/2 mutation who received a single agent PARPi in the real-world setting (N=21), 38% (8 of 21) patients initiated a PARPi after 16 weeks of platinum exposure without disease progression (i.e., platinum-sensitivity criteria fully met). However, only 14% (3 of 21) patients who reached this platinum sensitivity milestone initiated a PARPi before 2nd line.
- Among all patients with BRCA1/2 mutation (N=55) regardless of PARPi use, 16 weeks of platinum exposure without progression was observed in 73% (40 of 55) patients; however, only 49% (27 of 55) reached this milestone prior to initiating a 2nd line therapy.

Table 1. Clinical/Demographic Summary

Demographic and Clinical Features # Patients (%)	BRCA1/2-Mutated Cohort (N = 55)	PARPi-Users Subset (N = 33)
Cancer Type / Histology		
Pancreatic adenocarcinoma	53 (97.3%)	31 (94.0%)
Pancreatic acinar cell carcinoma	2 (2.7%)	2 (6.0%)
Sex		
Male	30 (54.5%)	16 (48.5%)
Female	25 (45.5%)	17 (51.5%)
Age at diagnosis		
<65	37 (67.3%)	21 (63.6%)
≥65	18 (32.7%)	12 (36.4%)
Median [IQR]	61 [54-66]	63 [55-67]
Stage at diagnosis		
IA/IB	2 (3.6%)	2 (6.1%)
IIA	5 (9.1%)	4 (12.1%)
IIB	9 (16.4%)	5 (15.2%)
III	5 (9.1%)	4 (12.1%)
IV	34 (61.8%)	18 (54.5%)
Ethnicity/race/background		
White (non-Hispanic)	31 (56.4%)	15 (45.5%)
Black	1 (1.8%)	1 (3%)
Asian	3 (5.5%)	2 (6.1%)
Hispanic	2 (3.6%)	2 (6.1%)
Ashkenazi Jewish	5 (9.1%)	2 (6.1%)
Not reported	13 (23.6%)	11 (33.3%)
Germline status of BRCA1/2 mutation		
Germline origin (likely or confirmed)	43 (78.2%)	27 (81.8%)
Somatic origin (likely or confirmed)	12 (21.8%)	6 (18.2%)
*Family history of BRCA-related cancers**		
Positive	31 (56.4%)	18 (54.5%)
Negative	13 (23.6%)	5 (15.2%)
Unknown	11 (20%)	10 (30.3%)

*Family history of BRCA-related cancers was defined as having a first-degree relative or at least 2 second-degree relatives with either pancreatic, ovarian, breast, or prostate cancer.

Methods

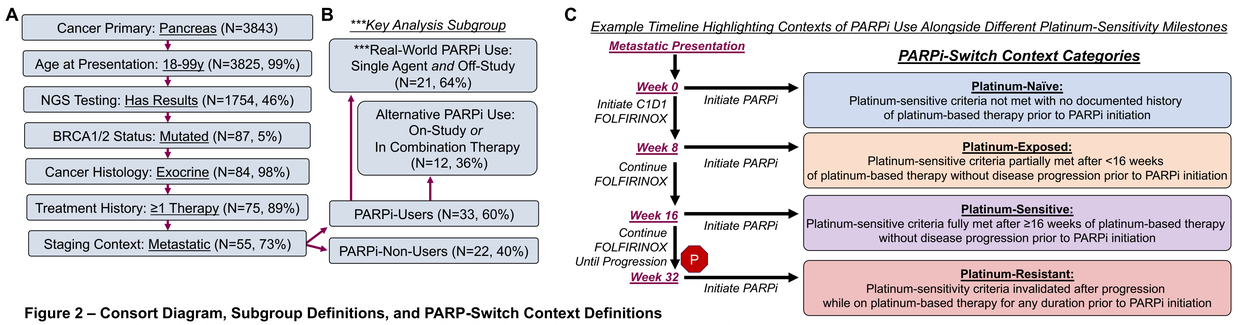

Figure 2 – Consort Diagram, Subgroup Definitions, and PARP-Switch Context Definitions
(A) Identification of patients with metastatic pancreatic cancer and BRCA1/2 mutation; (B) patients received PARPi either in a real-world scenario (i.e. where the concept of a maintenance switch was considered applicable) or in an alternative scenario (e.g. on a clinical trial or as part of a combination with other agents); (C) Real-world PARPi use occurred in various contexts regarding previous platinum use and disease progression status for the key analysis subgroup (Real-World PARPi-Users). Detailed definitions of four PARPi-Switch Context Categories are shown alongside an example timeline of platinum-based treatment history where PARPi initiation.

Methods

- Longitudinal records collected between 1/2012-12/2020 were analyzed for a real-world cohort of 55 mPaC patients with BRCA1 or BRCA2 mutations identified by commercial NGS testing who enrolled in Perthera's US registry. Treatment patterns including PARPi use and platinum-sensitivity were abstracted via physician notes across all lines of therapy.

Table 2. PARPi Usage Summary Relative to Platinum Sensitivity & Line of Therapy

More ← Platinum Exposure Before First PARPi Use (Real-World Scenarios Only) → Less

PARPi-Switch Context	# PARPi-Users (N = 21, %)	Treatment settings of first platinum use	Treatment settings of first PARP inhibitor use
Platinum-Naïve	2 (10%)	1st line (1); Censored (1)	1st line (2)
Platinum-Exposed	5 (24%)	Neoadjuvant (3); 2nd line (1); Censored (1)	Neoadjuvant (1); 1st line (1); 2nd line (3)
Platinum-Sensitive	8 (38%)	Neoadjuvant (1); 1st line (3); 2nd line (4)	1st line (3); 2nd line (3); 3rd line (2)
Platinum-Resistant	6 (28%)	1st line (4); 2nd line (2)	2nd line (1); 3rd line (3); 5th line (2)

Figure 3. Real-World Treatment Sequencing Highlights Heterogeneous Platinum-PARPi-Transitions

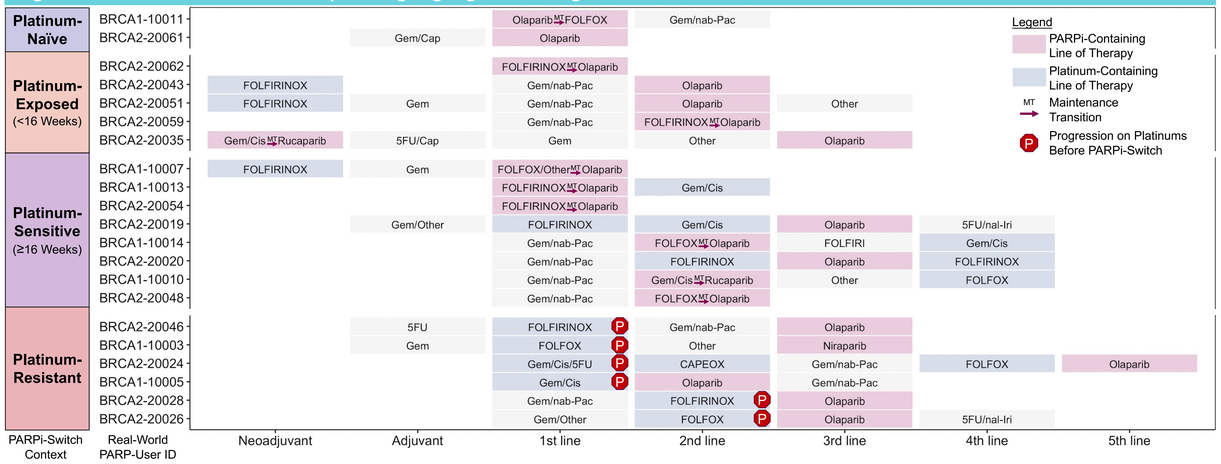

Figure 3. Therapy Implementations in 21 PARPi-Users with BRCA1/2-Mutated mPaC
Real-world treatment regimens documented before and/or after PARPi use (pink) are organized by line of therapy and implementation subgroup for PARPi use. Platinum-based therapies (without a PARPi) are highlighted in blue with platinum-sensitivity milestones above. Abbreviations: Gem (Gemcitabine), Cis (Cisplatin), nab-Pac (nab-Paclitaxel), 5FU (5-Fluorouracil), Cap (Capecitabine)

Disclosures

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