RUCAPANC: An Open-Label Phase 2 Trial of the PARP Inhibitor Rucaparib in Patients with Pancreatic Cancer and a Known Deleterious Germline or Somatic *BRCA* Mutation

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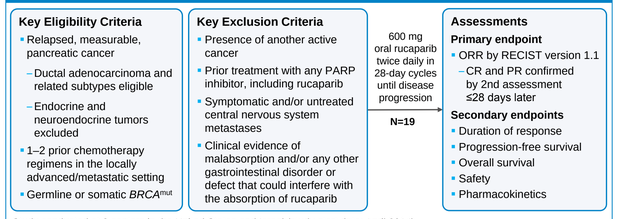
Abstract: 4110
Poster Board: 102

BACKGROUND

- Patients with pancreatic cancer have a poor prognosis and limited treatment options
- Approximately 17% of patients with pancreatic cancer have a germline or somatic defect in the BRCA pathway (eg, *BRCA1, BRCA2, ATM, or PALB2* mutation)[1,2]
- Aberrations in the DNA damage response pathway mediated by mutant *BRCA1* or *BRCA2* (*BRCA*) can be exploited therapeutically with poly(ADP-ribose) polymerase (PARP) inhibitors in genetically selected populations[3]
- Clinical benefit has been observed with PARP inhibitors in patients with advanced solid tumors and germline or somatic *BRCA* mutations[4-8]
  - Rucaparib, an oral PARP inhibitor, is active in patients with platinum-sensitive, relapsed, high-grade ovarian carcinoma and a germline or somatic *BRCA* mutation *(BRCA*^{mut}*)*[7]
- The phase 2 RUCAPANC study (NCT02042378) investigated the efficacy and safety of rucaparib in patients with pancreatic cancer and a known deleterious germline or somatic *BRCA*^{mut}
- Final results from RUCAPANC are presented

METHODS

Figure 1. Patient Eligibility and Study Design



Study conducted at 8 centers in the United States and Israel (study start date: April 2014).
CR, complete response; ORR, objective response rate; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors.

Statistical Analysis

- The safety population comprised all patients who received ≥1 dose of rucaparib; efficacy data are reported for the safety population unless otherwise specified
- Clopper-Pearson exact method was used to determine 95% confidence intervals (CIs)

RESULTS

- The last patient enrolled initiated treatment on February 18, 2015; the data cutoff date was April 15, 2016
- A total of 19 patients were enrolled and received ≥1 dose of rucaparib
- Patients started a median of 3 cycles (range, 1–18) of treatment
  - Patients received rucaparib for a median of 57 days (range, 2–504)
- Baseline characteristics are shown in **Table 1**

Table 1. Baseline Demographic and Disease Characteristics (N=19)

Parameter	Value
Median age (range), years	57 (41–75)
Male, n (%)	11 (57.9)
Median time from initial diagnosis (range), months	16.4 (4–44)
Time since diagnosis, n (%)[a]	
>3–6 months	1 (5.3)
>6–12 months	2 (10.5)
>12–24 months	11 (57.9)
>24 months	4 (21.1)
ECOG PS, n (%)	
0	4 (21.1)
1	15 (78.9)
Histological classification, n (%)	
Adenocarcinoma	18 (94.7)
Other	1 (5.3)
AJCC stage at study entry, n (%)	
Stage IIB	1 (5.3)
Stage III	1 (5.3)
Stage IV	15 (78.9)
Unknown	2 (10.5)
BRCA mutation type, n (%)	
Germline	15 (78.9)
Indeterminate[b]	4 (21.1)
BRCA status, n (%)	
BRCA1 mutation	4 (21.1)
BRCA2 mutation	15 (78.9)
Prior surgery, n (%)	10 (52.6)
Prior lines of chemotherapy, n (%)	
1 prior line	6 (31.6)
2 prior lines	11 (57.9)
3 prior lines	2 (10.5)

[a]Time since diagnosis was not provided for 1 patient (5.3%).
[b]Germline or somatic status could not be determined due to the absence of blood testing.
AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

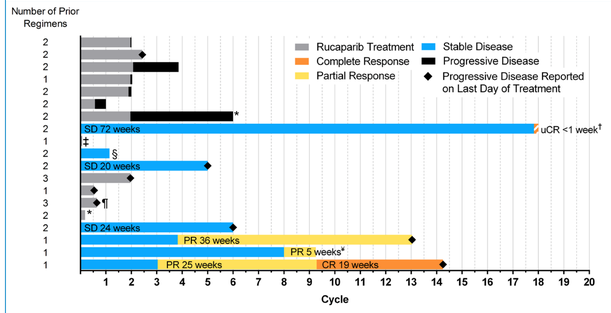
Efficacy

- The confirmed investigator-assessed Response Evaluation Criteria In Solid Tumors version 1 (RECIST) objective response rate (ORR) was 15.8% (95% CI, 3.4%–39.6%; 2 partial responses [PR] and 1 complete response [CR]), and the disease control rate was 31.6% (95% CI, 12.6%–56.6%) (**Table 2**, **Figure 2**)
  - All 3 patients with a confirmed response received only 1 prior line of therapy
  - One additional patient had an unconfirmed CR
  - Enrollment in the study was stopped because of a lack of response in the first 15 patients evaluated; the 3 responses occurred in the last 4 patients enrolled
- The duration of confirmed responses was 36 weeks (PR), 19 weeks (CR), and 5 weeks (PR)
  - One patient with stable disease (SD) was on study for 72 weeks and is continuing to receive rucaparib under an Individual Patient Investigational New Drug (IND) Application

Table 2. Investigator-Assessed Confirmed Responses (RECIST) in Patients with Pancreatic Cancer and *BRCA*^{mut} (N=19)

Overall best response	n (%)
Complete response (CR)	1 (5.3)
Partial response (PR)	2 (10.5)
Stable disease (SD)	4 (21.1)
Progressive disease (PD)	9 (47.4)
Not evaluable	3 (15.8)
Disease control rate (CR, PR, SD ≥12 weeks)	
All patients	6 (31.6)
Patients with ≤1 prior chemotherapy (n=6)	3 (50.0)

Figure 2. Treatment Duration for Patients with Pancreatic Cancer and a *BRCA* mutation (N=19)



Bars represent duration of rucaparib treatment for individual patients; plot is sorted by enrollment start date.
*Patient discontinued treatment for other reason. †Study was terminated, patient was rolled over to an Individual Patient IND application. ‡Patient discontinued due to investigator decision. §Patient discontinued due to AE and scan with stable disease was performed after last treatment day. ¶Patient discontinued due to AE and progressive disease. #Patient withdrew consent; PR was confirmed with a scan after last treatment day.
AE, adverse event; uCR, unconfirmed complete response.

Safety

- At the data cutoff date, no patients remained on study
  - Reasons for discontinuation of study treatment included disease progression (n=12; 63.2%), adverse event (AE; n=2; 10.5%), other (n=2; 10.5%), patient withdrawal of consent, investigator decision, and study terminated by sponsor (n=1 each; 5.3% each)
  - Once the study was terminated, 1 patient was rolled over to an Individual Patient IND
- All patients had at least one treatment-emergent AE
- Common treatment-emergent AEs (in ≥20% of patients) included nausea (63.2%) and anemia (47.4%) (**Table 3**)
  - The most common treatment-emergent grade ≥3 AE was anemia (31.6%)
- Four patients (21.1%) required a dose reduction
  - AEs leading to dose reduction included alanine or aspartate transaminase (ALT/AST) increased, fatigue, neutropenia, and thrombocytopenia (n=1 each; 5.3% each)
- Two patients (10.5%) discontinued treatment because of fatigue or thrombocytopenia (n=1 each; 5.3% each)
- Of the 3 deaths, 2 were from disease progression
  - One patient died from upper gastrointestinal hemorrhage and acute kidney injury, both of which were deemed to be unrelated to study treatment by the investigator

Table 3. Treatment-Emergent AEs Reported in ≥20% of Patients (N=19)

Parameter	Incidence, n (%)	
	Any grade	Grade 3–4
Nausea	12 (63.2)	2 (10.5)
Anemia	9 (47.4)	6 (31.6)
Abdominal pain	7 (36.8)	2 (10.5)
Fatigue	7 (36.8)	3 (15.8)
ALT/AST increased	6 (31.6)	2 (10.5)
Decreased appetite	6 (31.6)	0
Vomiting	6 (31.6)	2 (10.5)
Diarrhea	5 (26.3)	0
Thrombocytopenia[a]	5 (26.3)	2 (10.5)
Ascites	4 (21.1)	3 (15.8)
Constipation	4 (21.1)	0
Dysgeusia	4 (21.1)	0
Peripheral neuropathy	4 (21.1)	0

[a]Includes AEs of thrombocytopenia and platelet count decreased.
AEs were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.

CONCLUSIONS

- Rucaparib provided clinical benefit to several patients (disease control rate, 31.6%; 95% CI, 12.6%–56.6%) with advanced *BRCA*^{mut} pancreatic cancer
  - Less heavily pretreated patients derived durable clinical benefit, which warrants investigating rucaparib earlier in the treatment course of patients with *BRCA*^{mut} pancreatic cancer
- Rucaparib had an acceptable safety profile
- These findings will inform future rucaparib study designs in patients with advanced *BRCA*^{mut} pancreatic cancer

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ACKNOWLEDGMENTS

The authors would like to acknowledge all patients and their families and caregivers for participating in the RUCAPANC study, along with the investigators. We also thank Infusion Communications for providing editorial assistance, which was funded by Clovis Oncology, Inc. (Boulder, CO).