Population Exposure-Safety and Exposure-Efficacy Analyses for Rucaparib in Patients With Recurrent Ovarian Carcinoma From Study 10 and ARIEL2

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INTRODUCTION

- Rucaparib is a poly(ADP-ribose) polymerase (PARP) inhibitor that is approved for treatment and maintenance therapy of high-grade ovarian carcinoma (HGOC)
- We evaluated the correlations between rucaparib pharmacokinetic (PK) exposure and efficacy/safety in the treatment setting for patients with recurrent HGOC using pooled data from Study 10 (NCT01482715) and ARIEL2 (NCT01891344)

METHODS

- In Study 10, Part 1, patients with solid tumors received oral rucaparib 40–500 mg once daily (QD) or 240–840 mg twice daily (BID); in Study 10, Part 2, and ARIEL2, patients with relapsed HGOC received rucaparib 600 mg BID
- A population PK model[1] was developed and used to estimate the area under the concentration-time curve (AUC) and maximum concentration (C_{max}) for the exposure-efficacy and exposure-safety analyses shown in **Table 1**

Table 1. Overall Exposure-Efficacy and Exposure-Safety Analyses

	Exposure-efficacy analyses	Exposure-safety analyses
Analysis population	• Patients who received ≥1 rucaparib dose, had HGOC, a deleterious *BRCA* mutation, and ≥1 efficacy assessment	• Patients who received ≥1 rucaparib dose and had HGOC
Endpoints	• Investigator- and IRR-confirmed RECIST response • Composite endpoint of confirmed response by GCIG CA-125 criteria or RECIST response • Maximum percent change from baseline in sum of diameters of target lesions and in serum CA-125 • Progression-free survival • Duration of response	Laboratory variables: • Hepatic – grade ≥3 ALT, grade ≥3 AST, grade ≥2 bilirubin • Hematologic – grade ≥3 neutrophils, platelets, lymphocytes, and hemoglobin; maximum hemoglobin reduction • Other – grade ≥3 cholesterol, grade ≥2 creatinine Adverse events: • Grade ≥3 fatigue/asthenia, grade ≥3 nausea
PK exposure measure[a]	• Steady-state AUC normalized by actual dose for each patient up to the event of interest	• Steady-state C_{max} normalized by actual dose for each patient up to the event of interest
Model	• Linear logistic regression for binary endpoints • Linear regression for continuous endpoints • Cox regression for time-to-event endpoints	• Linear logistic regression for binary endpoints • Linear regression for continuous endpoints
Covariates[b]	• Age, race • Region • Germline *BRCA* mutation status • *BRCA1* vs *BRCA2* mutation • Number of prior chemotherapies • Progression-free interval since last platinum • ECOG PS • Baseline sum of diameters of target lesions	• Age, race • Germline *BRCA* mutation status • Number of prior chemotherapies • ECOG PS • Baseline albumin

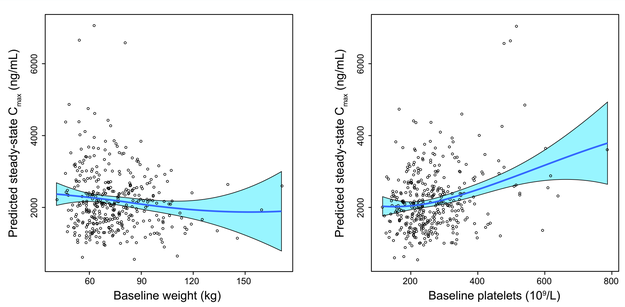
[a]A published population PK model was used to estimate actual dose-normalized average steady-state AUC and C_{max}.[1]
[b]Clinical covariates were tested in multivariate models.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the concentration-time curve; CA-125, cancer antigen 125; C_{max}, maximum concentration; ECOG PS, Eastern Cooperative Oncology Group performance status; GCIG, Gynecologic Cancer InterGroup; HGOC, high-grade ovarian carcinoma; IRR, independent radiologic review; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

- Exposure-QTcF prolongation analysis was conducted using data from patients in Part 1 of Study 10

RESULTS

- Rucaparib PK exposure was dose proportional[2] and not associated with baseline patient weight or baseline platelet counts (**Figure 1**)

Figure 1. Model-Predicted Steady-State C_{max} at 600 mg BID by Baseline Weight (Left) and Platelets (Right)



The points are individual model-predicted estimates of the maximum concentration (C_{max}) following a dose at steady state versus baseline weight or baseline platelets. The solid blue line is a local regression smooth showing the trend of the relationship. The blue shaded area around the blue line is the 5th to 95th percentile confidence interval around the trend.

Table 2. Exposure Summary in the Exposure-Efficacy and Exposure-Safety Analyses[a]

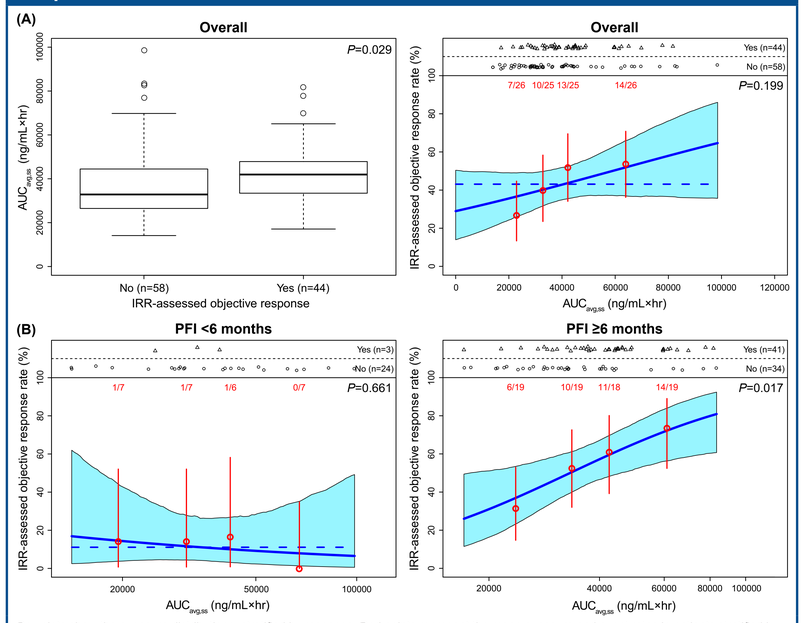
Variable	Exposure-efficacy analysis	Exposure-safety analysis
Patients (n)	121	393
Pharmacokinetics (n)[b]	117	375
$C_{max,avg,ss}$, mean (SD) [min, max] ng/mL	1712 (756) [166, 4413]	1839 (732) [75, 6254]
$AUC_{avg,ss}$, mean (SD) [min, max] ng/ml×hr	37145 (17140) [2328, 99524]	40200 (16767) [690, 141157]

[a]Overall exposure estimates over the full duration of treatment. [b]Number of patients with ≥1 evaluable PK concentration.
$AUC_{avg,ss}$, average steady-state area under the concentration-time curve; $C_{max,avg,ss}$, average maximum concentration at steady state.

Exposure-Efficacy Relationships

- Correlation was observed between $AUC_{avg,ss}$ and IRR-assessed RECIST response among HGOC patients with *BRCA* mutations and PFI ≥6 months (**Figure 2, Table 3**)
- No significant correlations were observed for other efficacy endpoints (**Table 3**)

Figure 2. Exposure-Response Relationships for IRR-assessed RECIST Response in Patients With a *BRCA* Mutation



Box plots show the exposure distributions, stratified by response. Red points represent the mean exposure and event rates in patients stratified by exposure quartile. Vertical red bars represent the 5th to 95th percentile confidence intervals on the event rate. Event numbers (patients with event/total patients) are displayed above each vertical bar. In each plot, the solid blue line is the logistic regression model fit for that patient subset. The shaded blue region represents 5th to 95th percentile confidence intervals on the predicted event rate. The horizontal blue dashed line shows the average response rate when the *P* value is >0.05. Regression analyses were conducted separately for patients with PFI <6 months and for patients with PFI ≥6 months.
$AUC_{avg,ss}$, average steady-state area under the concentration-time curve up until the relevant event; BID, twice daily; IRR, independent radiologic review; PFI, progression-free interval; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

Table 3. Exposure-Efficacy Relationships With Covariates in Patients With *BRCA* Mutations

Exposure metric[a]	Efficacy endpoint	*P* value for exposure: No covariate	*P* value for exposure: Adjusted for covariates[b]	Significant covariates (*P*<0.05)[c]
Dose	Investigator-assessed RECIST response	0.201	NA	NA
$AUC_{avg,ss}$	Investigator-assessed RECIST response	0.738	0.673	PFI, baseline sum of diameters of target lesions
$AUC_{avg,ss}$	IRR-assessed RECIST response	0.199	0.141	PFI
$AUC_{avg,ss}$	Maximum % change in sum of diameters of target lesions	0.297	0.451	PFI
$AUC_{avg,ss}$	Maximum % change in serum CA-125	0.705	0.498	PFI, baseline ECOG PS 1

[a]$AUC_{avg,ss}$ is the daily steady-state area under the concentration-time curve, corrected from the nominal dose to the average dose up until the relevant endpoint event. [b]"Adjusted" means that the model includes significant covariates. [c]The *P* value is the significance level for the exposure variable. Additional assessment using $AUC_{avg,ss}$ normalized by actual dose over the full duration of treatment also showed PFI as a significant covariate for GCIG CA-125/investigator-assessed RECIST response, PFS, and DOR. *BRCA* germline/somatic status was a significant covariate for DOR in the multivariate analysis.
AUC, area under the concentration-time curve; CA-125, cancer antigen 125; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GCIG, Gynecologic Cancer InterGroup; IRR, independent radiologic review; NA, not applicable; PFI, progression-free interval; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

Exposure-Safety Relationships

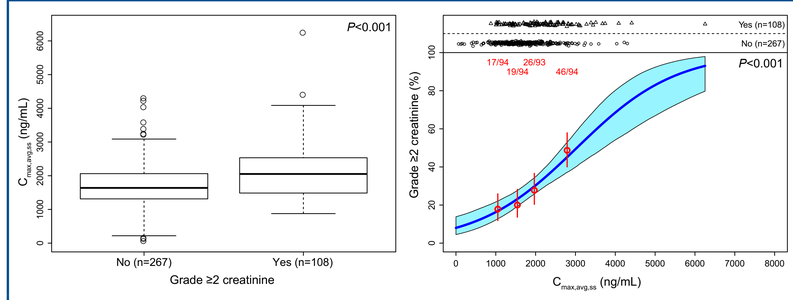
- In the exposure-safety analyses (n=375), patients received starting doses of rucaparib 40 mg QD up to 840 mg BID; most patients received the recommended phase 2 starting dose of 600 mg BID, with 27% and 21% of these patients receiving 1 and ≥2 dose reductions, respectively
- Positive correlations of exposure-response relationships were observed in selected safety endpoints (**Table 4, Figure 3**); while statistically significant covariates were identified, none were considered clinically significant

Table 4. Exposure-Safety Relationships With Covariates

Safety endpoint	*P* value for exposure: No covariate	*P* value for exposure: Adjusted for covariates[a]	Significant covariates (*P*<0.05)
ALT, grade ≥3	0.033*	0.025*	ECOG PS
AST, grade ≥3	0.027*	NA	None identified
Bilirubin, grade ≥2	0.723	NA	None identified
Neutrophils, grade ≥3	0.061	NA	None identified
Lymphocytes, grade ≥3	0.548	NA	None identified
Platelets, grade ≥3	0.040*	NA	None identified
Hemoglobin, grade ≥3	0.067	NA	None identified
Hemoglobin, CFB	0.001*	<0.001*	Albumin
Creatinine, grade ≥2	<0.001*	<0.001*	Age ≥65 y
Cholesterol, grade ≥3	0.088	NA	None identified
Fatigue/asthenia, grade ≥3	0.029*	NA	None identified
Nausea, grade ≥3	0.101	0.245	Albumin

*Denotes significant relationships (*P*<0.05). [a]"Adjusted" means that the model includes significant covariates.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CFB, change from baseline; ECOG PS, Eastern Cooperative Oncology Group performance status; NA, not applicable.

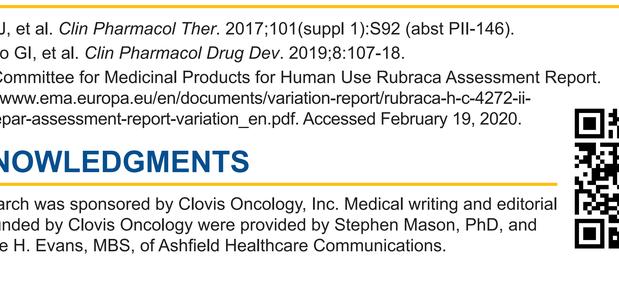
Figure 3. Exposure-Response Relationships for Creatinine



Box plots show the maximum concentration of rucaparib, stratified by grade ≥2 creatinine elevations.
Red points represent the mean exposure and event rates in patients stratified by exposure quartile. Vertical red bars represent the 5th to 95th percentile confidence intervals on the event rate. Event numbers (patients with event/total patients) are displayed above each vertical bar. Regression analyses were conducted for patients with grade ≥2 creatinine elevations. The solid blue line is the logistic regression model fit for that patient subset. The shaded blue region represents 5th to 95th percentile confidence intervals on the predicted event rate.
$C_{max,avg,ss}$, average maximum concentration at steady state.

- At the predicted median steady-state C_{max} following rucaparib 600 mg BID (n=54), the projected QTcF increase from baseline was 11.5 ms (90% CI, 8.77–14.2 ms; **Figure 4**)

Figure 4. QTcF Analysis Based on Data from Study 10 Dose Escalation



The points are triplicate mean ΔQTcF versus time-matched concentrations. The solid blue line is the line of best fit for mean ΔQTcF versus concentration using a linear mixed-effects model. The dark blue shaded band is the 5th to 95th percentile confidence interval in the mean fit. The light blue shaded band is the 5th to 95th percentile prediction interval of the data. The horizontal bar at the bottom of the plot is the 5th to 95th percentile range of steady-state average C_{max} data from patients with HGOC used in the exposure-safety analysis. The point is the median C_{max}, and the vertical dashed green and magenta lines indicate the median and 95th percentile concentrations, respectively. The projected ΔQTcF at the median and the 95th percentile C_{max} (labeled as "95% CI" in the figure text) are indicated by the green and magenta horizontal dashed lines, respectively.
BID, twice daily; CFB, change from baseline; C_{max}, maximum concentration; HGOC, high-grade ovarian carcinoma; QT, time from the start of the Q wave to the end of the T wave on an electrocardiogram; QTcF, QT corrected according to Fridericia's formula.

SUMMARY

- The exposure-response analyses supported the approved starting dose of rucaparib 600 mg BID with subsequent dose reductions following the occurrence of a treatment-emergent adverse event in platinum-sensitive, *BRCA*-mutated recurrent ovarian cancer
  - Higher rucaparib $AUC_{avg,ss}$ was associated with improved independent radiologic review-assessed response, but no significant correlations were observed for other efficacy endpoints
    - No statistically significant correlations have been observed between rucaparib $AUC_{avg,ss}$ and efficacy endpoints in patients with recurrent ovarian cancer associated with wild-type *BRCA* and high genomic loss of heterozygosity in rucaparib clinical trials[3]
  - Higher $C_{max,ss}$ was associated with higher incidence in a subset of clinical safety events
  - Clinically significant QTcF increase from baseline (ie, >20 ms) is unlikely following rucaparib 600 mg BID

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