Pharmacokinetics and Safety Following a Single Oral Dose of Niraparib in Patients With Moderate Hepatic Impairment

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Background

Context

Niraparib is a PARPi approved for:

- First-line maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy (USA)[1]
- Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy (USA and EU)[1,2]
- Treatment of adult patients with advanced, HRD-positive ovarian, fallopian tube, or primary peritoneal cancer who have received ≥3 prior chemotherapy regimens (USA)[1]

Niraparib is administered as 100-mg oral capsules, with or without food[1,2]

The recommended dose of **niraparib** for first-line maintenance treatment is 200 mg QD for patients weighing <77 kg or with a platelet count <150,000/μL and 300 mg QD for patients weighing ≥77 kg and with a platelet count ≥150,000/μL[1]

The recommended dose of **niraparib** for the latter two indications is 300 mg QD[1,2]

Niraparib PK

Niraparib is metabolized in the liver and eliminated primarily through the hepatobiliary and renal routes[3]

Prior characterization of **niraparib** PK demonstrated that systemic exposure increases in a dose-proportional manner[1,2,4]

A high volume of distribution and long elimination half-life may support the anti-cancer activity and recommended daily dose of **niraparib**[3]

Objective

The objective of this study (NCT03359850) was to characterize the PK and safety of **niraparib** in patients with moderate hepatic impairment (bilirubin >1.5 × to 3 × ULN and any AST elevation) versus patients with normal hepatic function to inform dosing recommendations

Methods

Phase 1 | Open-label | Non-randomized

Parallel-group | Single-dose* | Multicenter

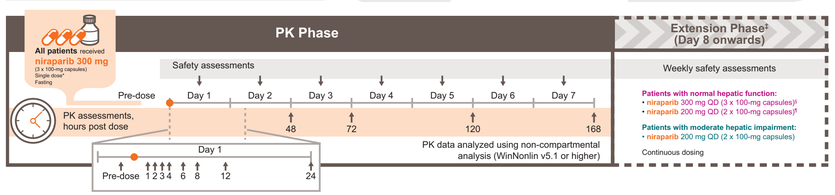
Advanced solid tumor[†]
≥18 years of age
ECOG PS 0 or 1

Normal hepatic function
BILI and AST ≤ ULN

Moderate hepatic impairment
BILI >1.5–3 times ULN and any AST elevation

Primary endpoint: PK
Key PK parameters: C_{max}, AUC_{last}, AUC_{inf}

Secondary endpoint: Safety (data shown are from PK phase only)



*Single-dose applies to PK phase of study only; [†]patient has failed standard therapy or standard therapy is not likely to provide meaningful benefit or the patient has refused standard therapy; [‡]if investigator believes patient may receive clinical benefit by continuing niraparib; [§]patients with screening body weight ≥77 kg and current platelet count ≥150,000/μL; [¶]patients with screening body weight <77 kg or current platelet count <150,000/μL.

Results

Baseline demographics, disease characteristics, and previous therapies

17 patients received **niraparib**

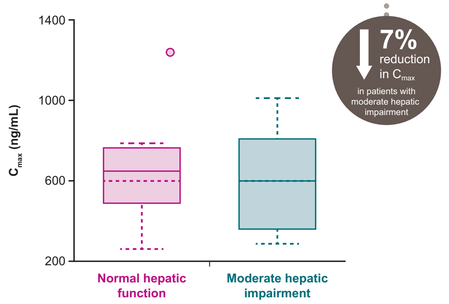
9 normal hepatic function

8 moderate hepatic impairment

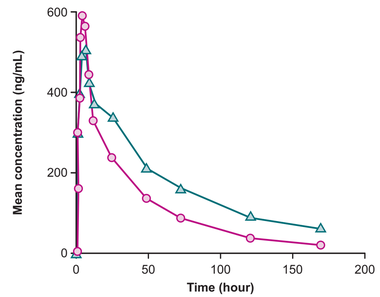
	Normal hepatic function	Moderate hepatic impairment
Median age	66 years	65 years
Female	2 (22%)	4 (50%)
Mean weight	91.2 kg	74.9 kg
Median albumin (range)	41 g/L (35–46)	29 g/L (22–38)
Tumor stage	78% stage IV 22% stage IVB	87% stage IV 13% stage IVB
Median prior lines of therapy (range)	5 (1–8)	4 (1–9)
ECOG PS	33% ECOG 0 67% ECOG 1	13% ECOG 0 87% ECOG 1
Median bilirubin (range)	6.8 μmol/L (5–14)	41.9 μmol/L (29–51)
Median ALT (range)	19 U/L (9–38)	51 U/L (29–94)
Median AST (range)	22 U/L (15–46)	80 U/L (47–313)

Niraparib PK profiles

Comparable maximum niraparib levels (C_{max}) irrespective of hepatic impairment

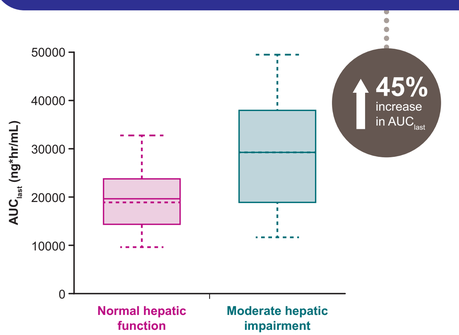


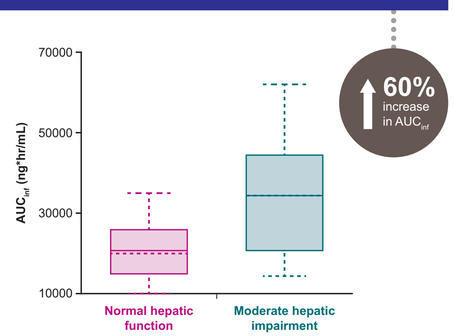
Modest increase in niraparib exposure in patients with moderate hepatic impairment



Solid lines represent mean values; dashed lines represent median values; upper and lower boxes represent middle two quartiles (ie, 50%); whiskers indicate minimum and maximum values.

Increased niraparib exposure (AUC) in patients with moderate hepatic impairment





Solid lines represent mean values; dashed lines represent median values; upper and lower boxes represent middle two quartiles (ie, 50%); whiskers indicate minimum and maximum values.

Safety

Safety data during the PK phase were consistent with the known safety profile for **niraparib**

Grade ≥3 TEAEs reported by patients

TEAE, n	Normal hepatic function (n=9)	Moderate hepatic impairment (n=8)
Any grade ≥3 TEAE*	**2**	**1**
Acute respiratory failure	1	0
Increased amylase	1	0
Increased AST	1	0
Increased lipase	1	0
Influenza	1	0
Pneumonia	1	0
Pulmonary hypertension	1	0
Hyperbilirubinemia	0	1
Hyponatremia	0	1
Lymphopenia	0	1

*Patients may have had more than 1 TEAE by preferred term; 2 patients in the normal hepatic function group and 1 patient in the moderate hepatic impairment group had at least one grade ≥3 TEAE.

Conclusions

- Preliminary data from the ongoing single-dose PK study demonstrated that moderate hepatic impairment did not meaningfully impact **niraparib** C_{max}
- On average, overall exposure of **niraparib** (AUC) was increased in patients with moderate hepatic impairment, compared with patients with normal hepatic function
- The increased exposure of **niraparib** in patients with moderate hepatic impairment did not noticeably alter the toxicity profile of **niraparib** in this population
- The safety profile for **niraparib** observed in this study was generally consistent with findings from previous clinical studies[5–7]
- These results warrant further analyses

Abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC_{inf}, area under the plasma concentration–time curve from time 0 extrapolated to infinity; AUC_{last}, area under the plasma concentration–time curve from time 0 to the time of the last quantifiable concentration; BILI, bilirubin; C_{max}, observed maximum plasma concentration; ECOG, Eastern Cooperative Oncology Group; HRD, homologous recombination deficiency; PARPi, poly (ADP-ribose) polymerase inhibitor; PK, pharmacokinetics; PS, performance status; QD, once daily; TEAE, treatment-emergent adverse event; ULN, upper limit of normal

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