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OPTIMUM: A randomized phase 2 study of maintenance olaparib (Ola) with or without durvalumab (Durva) in DDR gene-mutated advanced biliary tract cancer (aBTC)

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Background

Platinum-containing therapy is standard of care for pts with aBTC; however, no maintenance strategy has been validated following disease control. DNA damage repair (DDR) gene mutations are identified in pts with aBTC and PARP inhibitor maintenance may improve survival in this population.

Methods

OPTIMUM is a randomized, open-label, non-comparative, phase 2 trial. Eligible pts had aBTC, ECOG PS 0–1, at least one predefined somatic or germline DDR gene mutation, and no disease progression after ≥16 weeks of 1L platinum-based therapy. Pts were randomized 1:1 to Arm A (Ola 300 mg BID + Durva 1,500 mg IV Q4W) or Arm B (Ola 300 mg BID). The primary endpoint was 6-month PFS rate in the Full Analysis Set (FAS), and 62 patients were required to detect its improvement from a historical 48.0% to 69.3% (HR 0.5; one-sided α=0.05, power 80%).

Results

Between April 2022 and February 2026, 63 pts were enrolled, and 61 pts were included in the FAS (Arm A: n=32; Arm B: n=29). Baseline characteristics were well balanced between arms. The most frequent DDR alterations were ATM (34%), BRCA2 (25%) and BAP1 (25%). The 6-month PFS rate was 62.5% (95% CI, 46.8–74.7) in Arm A and 62.1% (45.5–74.9) in Arm B. Two-year OS rate in overall FAS was 40.1% (28.0–51.9). The core homologous recombination deficiency (cHRD) group (n=18, 30%) was significantly associated with better median PFS (20.5 vs. 7.4 mo, P=0.008) and OS (not reached vs. 16.5 mo, P=0.007) compared to others. Higher VAF in ctDNA at the time of study treatment showed negative correlation with PFS and OS. There was no new safety profile of Ola +/- Durva.Table: LBA22

Efficacy outcomes

	Overall FAS (arm A+B), n=61	Arm A (Ola+Durva), n=32	Arm B (Ola), n=29
PFS, median, months (90%CI)	8.2 (6.8–11.1)	7.7 (5.5–11.8)	8.2 (4.9–14.0)
6-month PFS rates, %	62.3 (51.2–71.5)	62.5 (46.8–74.7)	62.1 (45.5–74.9)
1-year PFS rates, %	37.2 (26.7–47.7)	31.7 (17.4–47.0)	41.1 (26.1–55.5)
OS, median, months	18.9 (15.7–27.2)	16.5 (11.8–19.9)	29.6 (15.7–NE)
1-year OS rates, %	70.5 (58.4–79.7)	64.3 (45.9–77.8)	75.9 (58.1–86.9)
2-year OS rates, %	40.1 (28.0–51.9)	25.0 (11.4–41.4)	53.6 (35.3–68.8)
ORR	27.5 (16.3–41.4)	30.0 (14.0–50.8)	25.0 (10.4–45.6)

Conclusions

Our findings suggest that a cHRD-defined DDR-mutated aBTC derives durable benefit from PARP inhibitor maintenance, supporting further development of HRD-targeted therapy in aBTC.

Clinical trial identification

NCT05222971.

Legal entity responsible for the study

The authors.

Funding

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Disclosure

C. Yoo: Financial Interests, Personal, Invited Speaker: Eisai, Ipsen, Servier, Roche, Novartis, BMS, Elevar Therapeutics, Boryung; Financial Interests, Personal, Advisory Board: AstraZeneca, Boehringer Ingelheim, Autem Therapeutics, Qurient, HLB; Financial Interests, Personal, Research Grant: AstraZeneca, Servier, Lunit, Boehringer Ingelheim; Financial Interests, Institutional, Research Grant: Genentech. All other authors have declared no conflicts of interest.

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