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Abstract CT267: First results of ART0380 (an ATR kinase inhibitor) with low dose irinotecan in advanced or metastatic solid tumors [REE]

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Abstract

Background:

Replication stress (RS) is a critical cancer vulnerability. ART0380 is an inhibitor of Ataxia-Telangiectasia and Rad3-related (ATR), the primary orchestrator of the cellular response to RS. This is the first clinical report of a development approach wherein tumor cells experience a triple combination of biological insults: induced RS by irinotecan, endogenous RS via ataxia-telangiectasia mutated (ATM) loss, and prevention of rescue from RS by ATR inhibition (NCT04657068).

Methods:

Patients (pts) with advanced cancers who had no satisfactory alternative treatment option received escalating doses of ART0380 (25mg to 400mg) on days 1-3 and 8-10 in combination with low dose irinotecan (60mg/m² or 85mg/m²) on days 1 and 8 of a 21-day cycle. Pts in dose expansion were selected based on ATM protein expression. Key objectives included safety, tolerability, and preliminary efficacy.

Results:

At the data cut-off (01Nov24), 87 patients were dosed with ART0380 + irinotecan. The recommended phase 2 dose (RP2D) was established as 200mg ART0380 on days 1-3 and 8-10 Skip to Main Content and 60mg/m2 irinotecan on days 1 and 8 of a 21-day cycle. At the RP2D (N=58), the median prior lines of therapy was 3 (range 1-7) with 59% of pts receiving prior irinotecan. The most common treatment related adverse events were neutropenia (53%), anemia (41%), fatigue

(33%) and diarrhea (31%). Grade≥3 related diarrhea, nausea and vomiting each occurred in 1 pt. By intent-to-treat (ITT) analysis, the confirmed objective response rate (ORR) was higher in pts with ATM protein loss by immunohistochemistry compared to those with tumors that expressed ATM protein (see <u>Table 1</u>). Further analyses with longer follow-up will be available for conference presentation.

Table 1:

Clinical activity of triple DDR challenge: High endogenous RS + Induced RS by low dose irinotecan + inhibition of cellular protection to RS by ART0380

ITT Population (H score)	Confirmed RECIST ORR% (n)	Median Duration of Response* months (range)	Т
ATM negative (0)	45% (9/20)	5.2 (1.4-10.7)	С
ATM low (1-50)	22% (4/18)	Not reached (3.5-7.9)	С
ATM negative and low (0-50)	34% (13/38)	Not reached (1.4-10.7)	С
ATM high (>50)	0% (0/13)	Not applicable	N
ATM unknown/not possible	0% (0/6)	Not applicable	N
All pts	23% (13/57 <u>^</u>)	Not reached (1.4-10.7)	(٤

Footnotes:

- * Median duration of response estimated using Kaplan Meier methodology. Responses are ongoing and durations will continue to mature.
- ^ 1 pt excluded from ITT due to early withdrawal of consent

Conclusions:

ART0380 and low dose irinotecan is well tolerated and suitable for long-term dosing. Clinically meaningful activity has been demonstrated and further refined via biomarker selection (45% confirmed RECIST response rate in patients with ATM negative cancers).

Citation Format:

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