Abstract #434350

Predictive role of homologous recombination deficiency (HRD) for irinotecan in combination with venadaparib, a novel PARP1/2 inhibitor as third- or fourth-line treatment in patients with advanced gastric cancer

Do-Youn Oh[1], Min-Hee Ryu[2], Keun-Wook Lee[3], Sun Young Rha[4], Seung Tae Kim[5], Syma Iqbal[6], Jeesun Yoon[1], Hyung-Don Kim[2], Ji-Won Kim[3], Jin Won Kim[3], Won Sik Lee[7], Min Ju Hong[7], Myongjae Lee[7], Eun-Jihn Roh[7], Kyoung Soo Ha[8]

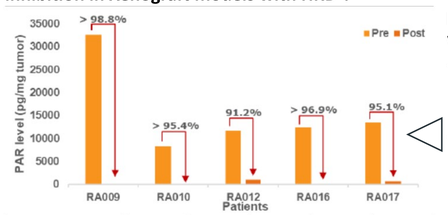
[1]Medical Oncology, Seoul National University Hospital, Seoul, Republic of Korea, Department of Oncology, [2]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, [3]Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea , [4]Yonsei Cancer Center, Yonsei University Heath System, Seoul, Republic of Korea, [5]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [6]University of Southern California - Norris Comprehensive Cancer Center and Hospital, Los Angeles, US, [7]Idience Co., Ltd., Seoul, Republic of Korea, [8]Idience Inc., Irvine, US

BACKGROUND

- There is unmet needs in 3L/4L treatment of advanced gastric cancer (GC) after 2L ramucirumab + paclitaxel treatment.
- Benefit of HRD screening in gastric cancer is unclear partly because of modest incidence. GOLD trial for ATM IHC enrichment nearly missed its primary endpoint.[1]
- Irinotecan, a TOP1 inhibitor, is an option of standard of care in advanced GC.[2]

Venadaparib, a next generation PARP inhibitor[3]

- Demonstrated potent PAR inhibition in vitro in HRD mutated cancer cell lines and tumor growth inhibition in Xenograft models with HRD².



Patients		RA009	RA010	RA012	RA016	RA017
Dose level		10 mg	20 mg	20 mg	20 mg	40 mg
Tumor Par level (pg/mg tumor)	Pre	32676.5	8403.3	11721.6	12489.2	13535.9
	Post > 3 days	BLQ	BLQ	1022.1	BLQ	666.4
% inhibition		> 98.8	> 95.4	91.2	> 96.9	95.1

* BLQ: below the limit of quantification (LLOQ: 390.6 pg/mg tumpr)

First in human study (NCT03317743)[4] of Venadaparib:

- Demonstrated PK linearity of venadaparib at 2 ~ 160 mg/d level with no dose limiting toxicities.
- Pharmacodynamic analysis in tumor biopsy samples demonstrated > 90% PAR inhibition with venadaparib ≥ 10 mg/d.
- 160 mg/d was determined as the RP2D of monotherapy.

Main questions

- To evaluate in vitro synergism of venadaparib plus irinotecan
- To evaluate the association of HRD and efficacy of irinotecan and venadaparib combined, in patients with metastatic GC who had failed at least 2 lines of therapy.

METHODS

MTT Assays To verify in vitro synergism between venadaparib & SN-38

Phase 1b trial (NCT04725994)

- Advanced gastric cancer patients ≥ 2 prior chemotherapy in South Korea, China and USA

Trial design:

Dose de-escalation: 3+3 design

- V 120 mg + I 100 mg/m²
- V 80 mg + I 100 mg/m²
- V 40 mg + I 100 mg/m²
- V 40 mg + I 75 mg/m²
- V 40 mg + I 50 mg/m²
- V 40 mg + I 100 mg/m² + G-CSF

Randomization → Dose Expansion: for Dose Optimization: MTD & lower dose levels N=15 per dose level

data presented

- V 20 mg + I 100 mg/m² + G-CSF
- V 10 mg + I 100 mg/m² + G-CSF

V: (Venadaparib) day 1~7
I: (Irinotecan), day 1
G-CSF: (prophylactic pegylated G-CSF), day 2

Endpoints:

- RECIST 1.1 tumor response, MTD
- Exploratory ctDNA analysis (Guardant OMNI Panel)

Guardant OMNI® Panel (Redwood, CA) has 500 genes with 46 HRD genes below including ATM, BRCA1/2

ATM, ATR, ATRX, BARD1, BRCA1, BRCA2, BRIP1, CHEK1, CHEK2, CTCF, DAXX, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, HDAC2, KEAP1, MRE11, NBN, NF1, PALB2, PBRM1, PTEN, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RB1, SETD2, SMAD2, SMAD3, SMAD4, STAG2, TP53, TSC1, TSC2, XRCC2, XRCC3

MAIN FINDINGS

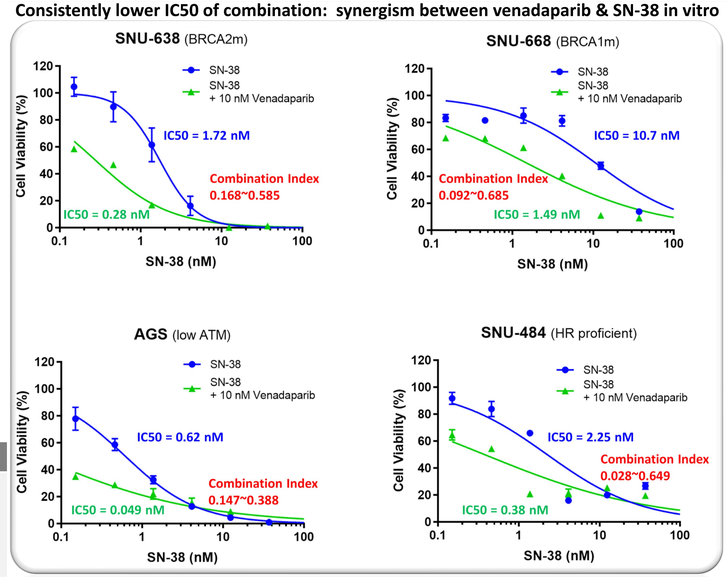
- Venadaparib as low as 10nM (equivalent to < 10 mg/d human dose) plus Irinotecan suggests synergism in vitro.
- Venadaparib plus Irinotecan showed strong efficacy signal, ORR of 36.4% in all-comer and 60%, in patients with HRD (by ctDNA) in 3L/4L treatment of advanced gastric cancer.

idience
Precision Medicine Matters
www.idience.com
Idience Co., Ltd.
2, Baumoe-ro 27-gil, Seocho-gu, Seoul, Korea 06752
Mail: info@idience.com
Tel: +82 2 526 3622
Fax: +82 2 526 3620

RESULTS

MTT Assays

Consistently lower IC50 of combination: synergism between venadaparib & SN-38 in vitro



Phase Ib Trial Demographics

Characteristics (Total N=26)	N (%)
Sex	
Male	21 (80.8)
Female	5 (19.2)
Age (range)	60.8 (41–74)
Prior chemotherapy	
Number of prior treatment	
2	16 (61.5)
3	10 (38.5)
Platinum	26 (100)
Anti-PD-1	9 (34.6)
RAMPTX	21 (80.7)
Anti-HER2	2 (7.7)
Prior surgery	
Yes	13 (50)
No	13 (50)
HRR mutation (by ctDNA)	1 BRCA2m 4 ATMm

Phase Ib Trial Safety

- Neutropenia is the main SAE during de-escalation in dose finding cohort
- MTD – 20 mg Venadaparib + 100 mg/m² Irinotecan with no DLT

Phase Ib Trial Efficacy

	Progression Free Survival Median (95%CI)	Overall Survival Median (95%CI)
All (N=26)	4.9 (2.7-5.6)	8.0 (6.1-12.0)
Irinotecan @100 mg/m² (N=11)*	5.6 (2.5 – NR)	8.1 (3.1-NR)
HRD (N=5)	NR	NR

* Venadaparib dose range: 40 ~ 120 mg/d

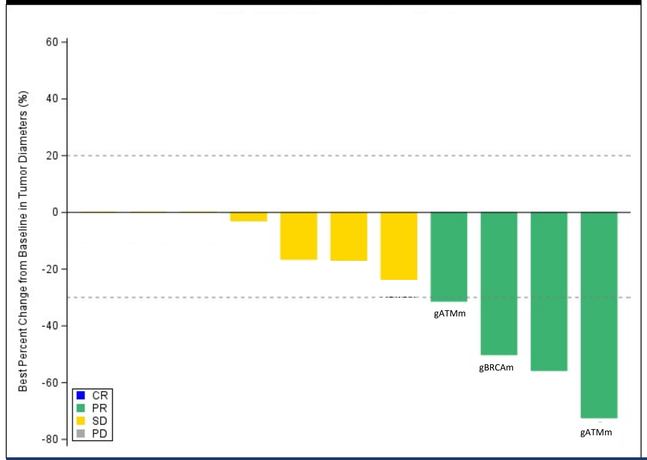
FUTURE DIRECTION FOR RESEARCH

- 3L/4L gastric cancer patients can be benefitted by Venadaparib + Irinotecan
- Gastric cancer with HRD assessed by ctDNA can be a good treatment target for PARP inhibitor + TOP1 inhibitor
- For dose optimization, randomized dose expansion phase including lower dose of venadaparib + irinotecan ± G-CSF is on-going.

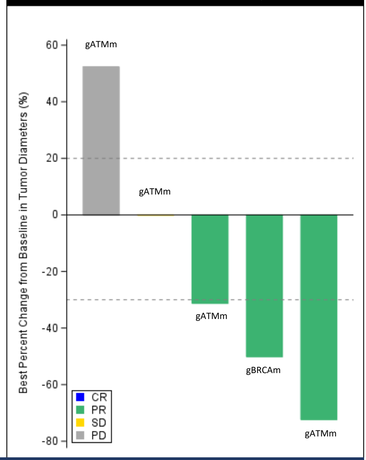
REFERENCES

1. Lancet Oncol. 2017 Dec;18(12):1637-1651.
2. NCCN Clinical Practice Guidelines in Oncology - Gastric Cancer. Version 2.2023.
3. Mol Cancer Ther. 2023 Mar 2;22(3):333-342.
4. ClinicalTrials.gov Identifier (NCT03317743)

Phase Ib Trial Waterfall: Irinotecan @ 100 mg/m2



Phase Ib Trial Waterfall: HRD patients



- Objective response rate (ORR, %) of 11 patients with Irinotecan @100mg/m²: 36.4%
- In the five patients with HRD, ORR was 60% and mPFS not reached.