Results from the first-in-human study of ATR inhibitor, IMP9064 monotherapy dose escalation in patients with advanced solid tumors

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Chia-Chi Lin[1], Reva Elaine Schneider[2], Martin Gutierrez[3], Lin Shen[4], Ki Chung[5], Deborah Doroshow[6], Bo Gao[7], Michael Millward[8], Chih-Yi Hsieh[9], Cong Xu[9], Sui Xiong Cai[9], Ye Edward Tian[9], Lan Liu[9], Chunfeng Shen[9], Yusi Tan[9], Yanna He[9], Congcong Zhang[9], Liangliang Li[10], Meng Ma[9], Li Xu[9]

[1]Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan [2]Medical Oncology Department, Mary Crowley Cancer Research, Dallas, United States of America, [3]Medical Oncology Department, John Theurer Cancer Center - Hackensack University Medical Center, Hackensack, United States of America [4]GI Oncology Department, Peking University Cancer Hospital and Institute, Beijing, China [5]Clinical Research, Prisma Health System - Upstate - Institute for Translational Oncology Research, Greenville, United States of America [6]Division of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, United States of America [7]Haematology and Cancer Care Center, Blacktown Hospital and University of Sydney, Blacktown, NSW, Australia [8]Oncology, Linear Clinical Research, Perth, WA, Australia [9]Clinical development, IMPACT Therapeutics, Inc. (Shanghai), Shanghai, China [10]Medical, IQVIA RDS(Shanghai) Co.,Ltd. Beijing Branch, Beijing, China

BACKGROUND

- Ataxia telangiectasia and Rad3-related (ATR) kinase is a master regulator in response to replication stress (RS), contributing to both genomic integrity in normal cells and replication stress tolerance in cancer cells[1].Selective inhibition of ATR can lead to cytotoxicity due to oncogene-induced RS, resulting in cell death[2].
- IMP9064 is a potent, orally administrated, selective ATR inhibitor with a nano-molar range potency and inhibitory activity against various cancer cells. Both in vitro and in vivo studies show IMP9064 increases effectiveness of cancer treatments, either as monotherapy or synergize with poly (ADP-ribose) polymerase (PARP) inhibitors.
- Here, we reported monotherapy dose escalation results of this open-label, phase 1/2 study (NCT05269316).

STUDY SCHEMA

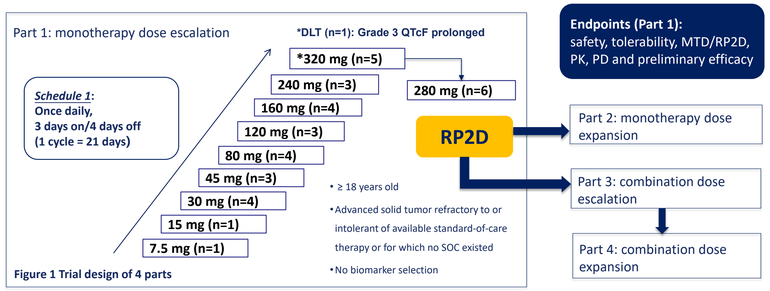


Figure 1 Trial design of 4 parts

Abbreviations: DLT, dose-limiting toxicity; RP2D, recommended phase 2 dose; MTD, maximum tolerated dose; PK, pharmacokinetics; PD, pharmacodynamic

CHARACTERISTICS

Table 1 Baseline characteristics

Demographics	Patients (%)	Demographics	Patients (%)
Gender, n (%)		Lines of prior anti-cancer therapy, n (%)	
Female	20 (58.8)	< 3	15 (44.1)
Male	14 (41.2)	≥ 3	19 (55.9)
Median Age(years), range	62.0 (19,81)	Tumor type	
Race, n (%)		Colorectal carcinoma	6 (17.6)
Asian	17 (50.0)	Endometrial Carcinoma	5 (14.7)
White	16 (47.1)	Uterine leiomyosarcoma	4 (11.8)
Black or African American	1 (2.9)	Lung Cancer	3 (8.8)
ECOG, n (%)		Ovarian Cancer	2 (5.8)
0	19 (55.9)	Cholangiocarcinoma	2 (5.8)
1	15 (44.1)	Others	12 (35.3)

- As of 19Jun, totally 34 patients enrolled.
- Median age 62.0 years.
- 55.9% of patients received ≥ 3 lines of therapy.
- Most common tumor types:
  - colorectal carcinoma
  - endometrial carcinoma
  - uterine leiomyosarcoma

PK

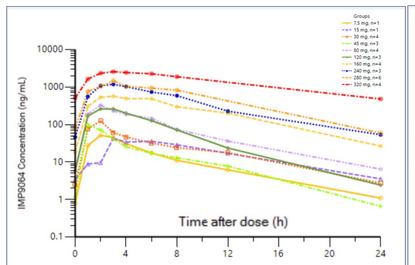


Figure 2 Semi-log of mean IMP9064 plasma concentration at steady state

PK/PD

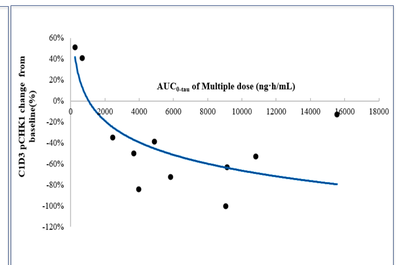


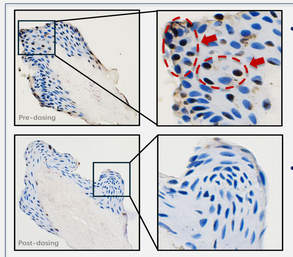
Figure 3 Correlation between IMP9064 $AUC_{0\text{-}tau}$ and pCHK1 change from baseline at steady state

- Rapidly absorbed; geometric mean half life was within 7 hours for most doses; approximately linear PK profiles (Figure 2).
- The PK/PD relationship demonstrates an exposure-dependent target engagement, i.e. %pCHK1 inhibition increased as the exposure ($AUC_{0\text{-}tau}$) increased. (Figure 3).

CONCLUSIONS

- IMP9064 demonstrated a favorable safety profile and is well-tolerated when dosed intermittently (*Schedule 1*, once daily, 3 days on/4 days off) in AST.
- IMP9064 demonstrated rapid absorption, with median T_{max} ranged from approximately 1 to 4 hours both in single and multiple doses. IMP9064 exposure (AUC) and C_{max} increases approximately proportionally within dose ranging from 7.5 mg to 320 mg . There was minimal accumulation for IMP9064 in plasma after continuous dosing (*Schedule 1*).
- IMP9064 has shown preliminary clinical efficacy signal and sustained clinical benefit in late-stage AST. 1 partial response observed at the dose level of 280 mg (*Schedule 1*).
- The logarithmic regression analysis of the PK/PD relationship between the AUC of IMP9064 in plasma and the inhibition of pCHK1 activation at steady state across various dose cohorts demonstrates an exposure-dependent target engagement.
- RP2D of *Schedule 1* for IMP9064 monotherapy declared as 280 mg.
- Clinical expansion of IMP9064 as monotherapy ongoing.

pCHK1 expression in hair follicle

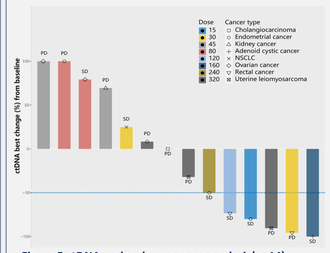


- Hair follicle sections were scored quantitatively for PD marker pCHK1 by Immunohistochemistry (IHC) .
- pCHK1 was showed as darkly stained in nuclei.

Figure 4 Immunohistochemistry (IHC) staining of pharmacodynamics marker pCHK1 in hair follicles before and after dosing（240mg cohort）

ctDNA molecular response

- Molecular response were observed in 6/14 (43%) patients.

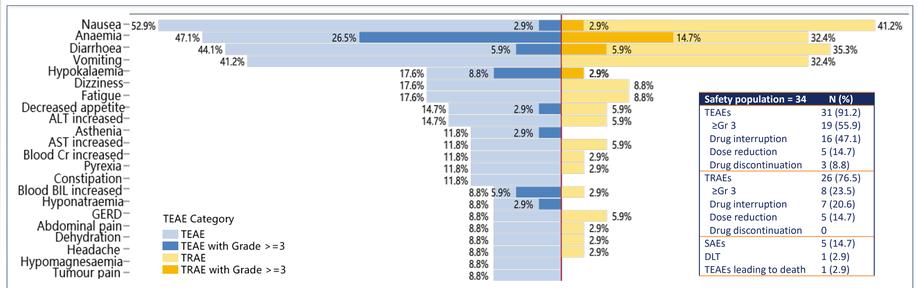


- Reduction of somatic allele frequencies from baseline by more than 50% is identified as molecular response.
- Baseline refers to the timepoint of Predose Day 1 during single dose period.
- Variation changes were capped no more than 100%.

Figure 5 ctDNA molecular response analysis(n=14)

SAFETY

- 1 DLT (Grade 3 QTcF prolonged) reported from 320 mg dose level: absolute value of pre-dose ECG QTcF interval 500.7 ms on C1D3, with +31.1 ms changed from baseline, and recovered on the same day after observation.
- TEAEs with incidence ≥ 8% (reported in ≥ 3 patients) are listed in Figure 6. The most common TEAEs (incidence ≥ 20%) included nausea, anaemia, diarrhoea and vomiting. The most common TRAEs (incidence ≥ 10%) were nausea, diarrhoea, vomiting and anaemia. The Grade ≥ 3 TRAEs reported in ≥ 2 patients were Grade 3 anemia and diarrhoea. No TRAEs with grade 4 or grade 5, or leading to drug discontinuation occurred.



Safety population = 34	N (%)
TEAEs	31 (91.2)
≥Gr 3	19 (55.9)
Drug interruption	16 (47.1)
Dose reduction	5 (14.7)
Drug discontinuation	3 (8.8)
TRAEs	26 (76.5)
≥Gr 3	8 (23.5)
Drug interruption	7 (20.6)
Dose reduction	5 (14.7)
Drug discontinuation	0
SAEs	5 (14.7)
DLT	1 (2.9)
TEAEs leading to death	1 (2.9)

Figure 6 Butterfly Plot of Adverse Events

Abbreviations: ECG, electrocardiogram; TEAE, treatment emergent adverse event; TRAE, treatment related adverse event; SAE, severe adverse event; Gr, grade

EFFICACY

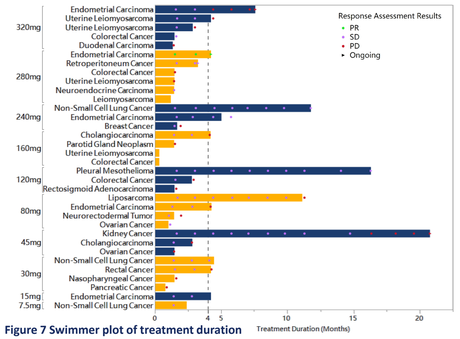


Figure 7 Swimmer plot of treatment duration

Abbreviations: DCR, disease control rate; CBR, clinical benefit rate; PFS, progression-free survival

- Of 34 patients enrolled, 31 patients had received at least one post-treatment tumor assessment.
- As of 19Jun, 1 patient had confirmed partial response (PR) from 280 mg dose level and 20 patients had stable disease (SD) as their best responses.
- 4 patients experienced prolonged stable disease with more than 24 weeks of treatment.
- DCR 64.5% and CBR (PR+SD ≥ 4 months) 35.5%.
- Median PFS 4.0 months.

- 62Y, female, endometrial cancer with ARID1A/CTNNB1/PTEN mutations.
- Completed platinum-containing neoadjuvant chemotherapy and pembrolizumab plus lenvatinib as 1st line therapy before enrollment.
- PR with rapid decrease in the target lesion by 31.8% at the 6th week scan, and by 45.5% at the 12th week scan, which is ongoing. One of the target lesions in the right lower lobe (lung) is shown in Figure 8.

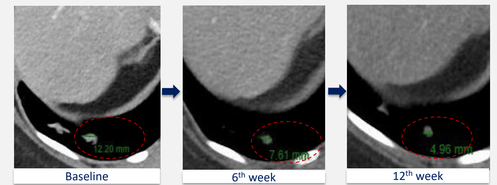


Figure 8 Target lesion in right lower lobe measurement

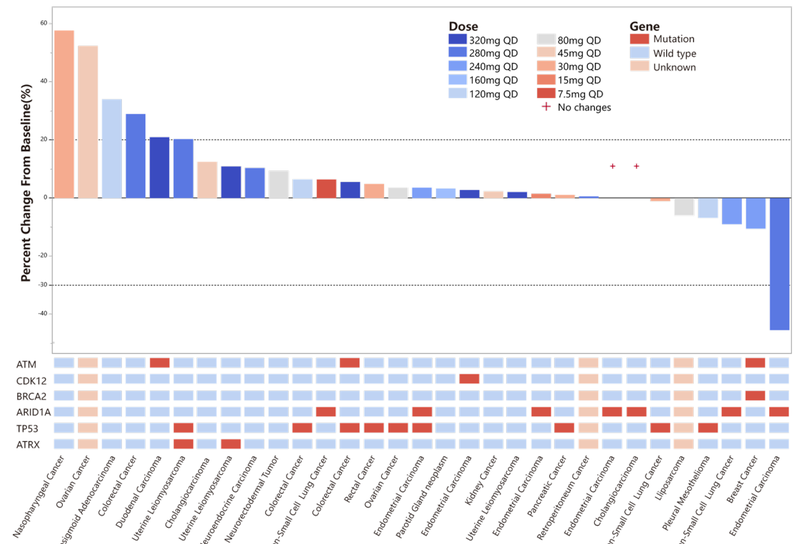


Figure 9 Best Response in Target Lesions and individual gene mutations（N=31）

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