Poster No. 482P

Safety, pharmacokinetic and pharmacodynamic profiles of the WEE1 inhibitor IMP7068 in patients with advanced solid tumors

C.-C. Lin[1], J. Grewal[2], D. Sommerhalder[3], L.-Y. Bai[4], G.-L. Li[5], R. Schneider[6], L. Shen[7], Y.-M. Yeh[8], R. Yin[9], H.-C. Hsu[10], J. Baranda[11], C.-Y. Hsieh[12], S.X. Cai[13], Y.E. Tian[14], N. Ma[13], H. Xia[12], C.-C. Zhang[12], B.-Y. Li[12], M. Zhang[12], Z.-X. Yu[12]

[1]Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan; [2]Medical Oncology, Norton Cancer Institute, Louisville, KY, USA; [3]Medical Oncology and Hematology, NEXT Oncology, San Antonio, TX, USA; [4]Division of Hematology and Oncology, China Medical University Hospital, Taichung, Taiwan; [5]Gynaecological Oncology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [6]Outpatient Evaluation and Treatment Center at Texas Oncology, Mary Crowley Cancer Research Center, Dallas, TX, USA; [7]Department of Digestive Oncology, Beijing Cancer Hospital, Beijing, China; [8]Oncology, NCKUH – National Cheng Kung University Hospital, Tainan City, Taiwan; [9]Department of Oncology and Chemoradiotherapy, West China Second University Hospital, Sichuan University/West China Women's and Children's Hospital, Chengdu, China; [10]Oncology, Chang Gung Medical Foundation – Linkou Branch, Taoyuan City, Taiwan; [11]Medical Oncology Department, KUMC – University of Kansas Clinical Research Center, Kansas City, KS, USA; [12]Clinical Development, IMPACT Therapeutics, Inc. (Shanghai), Shanghai, China; [13]Development, IMPACT Therapeutics, Inc. (Shanghai), Shanghai, China; [14]Research, IMPACT Therapeutics, Inc. (Shanghai), Shanghai, China

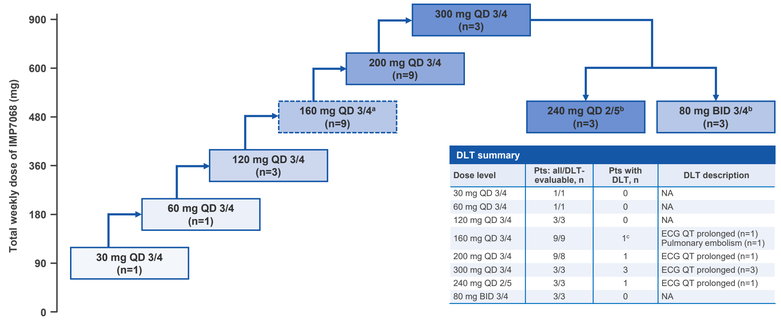
Introduction

- The G1/S and G2/M cell-cycle checkpoints, which are largely regulated by transcription factor p53 and WEE1 kinase, respectively, are key players in cellular DNA-damage repair (DDR); their role is to mitigate the risk of the genetic instability and chromosomal aberrations that drive many cancers[1,2]
- The G2/M checkpoint is activated in the presence of G1/S checkpoint inactivation, increased DNA damage, or replicative stress[1,3]
- Inhibition of WEE1 leads to failure of the G2/M checkpoint, subsequent accumulation of cellular DNA damage, mitotic catastrophe, and cell death[1]; a synthetically lethal situation arises when there is simultaneous disruption of the G1/S checkpoint, for example in cells harboring mutations in genes involved in DDR, such as *TP53* or *KRAS*, which are highly prevalent in many cancers[1–4]
- DDR synthetic lethality approaches have demonstrated some success in patients (pts) with advanced solid tumors[5]
- The potent, selective, orally available WEE1 inhibitor IMP7068 has shown antitumor activity in preclinical models, with limited off-target activity[6]
- A dose-escalation and dose-expansion study was conducted to evaluate the safety and efficacy of IMP7068 in pts with advanced solid tumors (NCT04768868)
- The findings of the dose-escalation stage are presented

Methods

- This open-label, phase 1 study enrolled adult pts with histologically or cytologically confirmed advanced/metastatic solid tumors that were refractory or intolerant to standard treatment, or for which no standard treatment exists
- Pts received oral doses of IMP7068 at planned doses of 30, 60, 120, 200, 300, or 400 mg once daily (QD) for 3 days, followed by 4 days off per week for each 21-day cycle (3/4) (**Figure 1**)
  - A 160 mg QD dose cohort was added based on Safety Monitoring Committee (SMC) review of pharmacokinetic (PK) data from the 120 mg dose cohort, to better characterize the safety and antitumor activity of IMP7068
  - Other schedules were also evaluated upon approval from the SMC after thorough review of all available data from the prior dose schedule(s), leading to commencement of two additional cohorts: 240 mg QD for 2 days on, 5 days off (2/5) and 80 mg twice daily (BID) on a 3/4 schedule
- An accelerated titration design was used for the 30 mg and 60 mg dose levels, and an i3+3 design for all others
- The primary objective of this study was to determine the safety, tolerability, and recommended phase 2 dose (RP2D) of IMP7068 monotherapy
- Secondary objectives included characterization of the PK profile of single and repeated doses of IMP7068, and preliminary evaluation of antitumor efficacy with repeated dosing in pts with advanced solid tumors

Figure 1: Dose-escalation scheme and DLT summary



DLT summary

Dose level	Pts: all/DLT-evaluable, n	Pts with DLT, n	DLT description
30 mg QD 3/4	1/1	0	NA
60 mg QD 3/4	1/1	0	NA
120 mg QD 3/4	3/3	0	NA
160 mg QD 3/4	9/9	1[c]	ECG QT prolonged (n=1) Pulmonary embolism (n=1)
200 mg QD 3/4	9/8	1	ECG QT prolonged (n=1)
300 mg QD 3/4	3/3	3	ECG QT prolonged (n=3)
240 mg QD 2/5	3/3	1	ECG QT prolonged (n=1)
80 mg BID 3/4	3/3	0	NA

[a]The 160 mg QD dose was added based on the SMC review of PK data from the 120 mg dose. [b]Doses added following the SMC review of PK/PD and safety data; additional schedules will be explored in the escalation phase. [c]Both DLTs occurred in one patient simultaneously.
2/5, doses administered once daily for 2 days followed by 5 days off per week over each 21-day cycle; 3/4, doses administered once daily for 3 days followed by 4 days off per week over each 21-day cycle; BID, twice daily; DLT, dose-limiting toxicity; ECG, electrocardiogram; PD, pharmacodynamic; PK, pharmacokinetic; pts, patients; QD, once daily; SMC, Safety Monitoring Committee.

Results

Patient demographics and baseline characteristics

- At the data cut-off date of July 18, 2022, 32 pts had been enrolled across eight dose cohorts of IMP7068 30–300 mg QD 3/4, 80 mg BID 3/4, and 240 mg QD 2/5
- 27 pts had discontinued the study; five pts remained on the study
- The population was heavily pre-treated, with 71.9% having received ≥3 prior lines of anticancer therapy and 53.1% having received ≥4 lines (**Table**)
- The most common malignancies among the total study population were colorectal cancer (n=11, 34.4%) and ovarian cancer (n=10, 31.3%)

Table: Demographic and baseline characteristics of the total study population

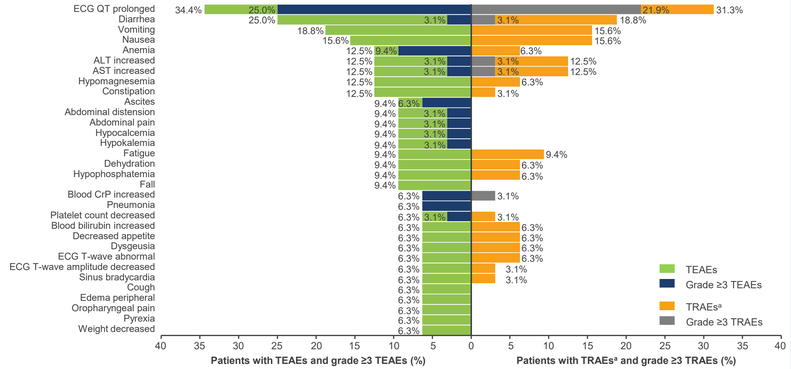
		Total population, N=32
Age, median (range)	Years	60 (20–75)
Sex, n (%)	Female	22 (68.8)
	Male	10 (31.3)
Race, n (%)	White	10 (31.3)
	Black or African American	3 (9.4)
	Asian	19 (59.4)
ECOG PS, n (%)	0	13 (40.6)
	1	19 (59.4)
Prior lines of therapy for advanced/metastatic disease, n (%)[a]	1	4 (12.5)
	2	4 (12.5)
	3	6 (18.8)
	4	1 (3.1)
	≥5	16 (50.0)
Primary diagnosis (in ≥2 patients), n (%)	Colorectal cancer	11 (34.4)
	Ovarian cancer[b]	10 (31.3)
	Uterine cancer[c]	4 (9.4)
	Other[d]	7 (21.9)

[a]The number of prior lines of therapy was unknown for one pt. [b]Includes ovarian, fallopian tube, and primary peritoneal cancer. [c]Includes uterine and endometrial cancer. [d]Includes cholangiocarcinoma, adenoid cystic carcinoma, osteocarcinoma, pancreatic ductal adenocarcinoma, parotid gland cancer, solitary fibrous tumor, and thymoma (n=1 [3.1%] for each).
ECOG PS, Eastern Cooperative Oncology Group performance status.

Safety

- Six pts experienced DLT events (**Figure 1**)
- 29 (90.6%) pts reported ≥1 treatment-emergent adverse event (TEAE), which was predominantly grade 1–2 (**Figure 2**)
  - The most common TEAEs were ECG QT prolonged (n=11, 34.4%) and diarrhea (n=8, 25.0%)
- TEAEs that were considered treatment-related (TRAEs) occurred in 21 (65.6%) pts and were mostly grade 1–2 (**Figure 2**)
  - The most common TRAEs were ECG QT prolonged (n=10, 31.3%) and diarrhea (n=6, 18.8%)
  - TRAEs led to dose reduction in one (3.1%) pt, dose interruption/delay in four (12.5%) pts, and study drug withdrawal in six (18.8%) pts
- Serious adverse events were reported in seven (21.9%) pts overall, and only for pts in the 120, 160, and 200 mg QD, and 80 mg BID dose cohorts
- There were no TEAE- or TRAE-related deaths

Figure 2: TEAEs and TRAEs, any grade and grade ≥3 (NCI CTCAE v5), by preferred term

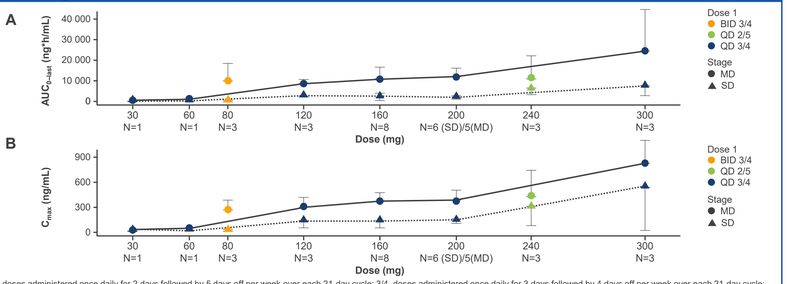


[a]Treatment-emergent adverse events that were considered by the investigator to be related to IMP7068.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CrP, creatine phosphokinase; ECG, electrocardiogram; NCI CTCAE v5, National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

PK/PD

- PK modeling predicted that a BID regimen would increase IMP7068 exposure versus the same QD dose and would be more favorable with regard to concentration-dependent adverse events (**Figure 3A, B**)
- The exposure (area under the time–concentration curve) of IMP7068 in the 80 mg BID 3/4 and 240 mg QD 2/5 dose cohorts was similar to that in the 160 mg QD 3/4 dose cohort (**Figure 3A**), and the maximum plasma concentration of IMP7068 with the 80 mg BID dose was lower than with the 160 mg QD 3/4 dose (**Figure 3B**)
- The PK data indicate good oral exposure up to doses of 300 mg QD and 80 mg BID
- Levels of the PD marker phosphorylated cyclin-dependent kinase 1 decreased by ≥50% after IMP7068 doses of 160–200 mg QD and 80 mg BID

Figure 3: (A) IMP7068 exposure and (B) maximum plasma concentration of IMP7068 by dosing schedule, after a single dose and after multiple doses

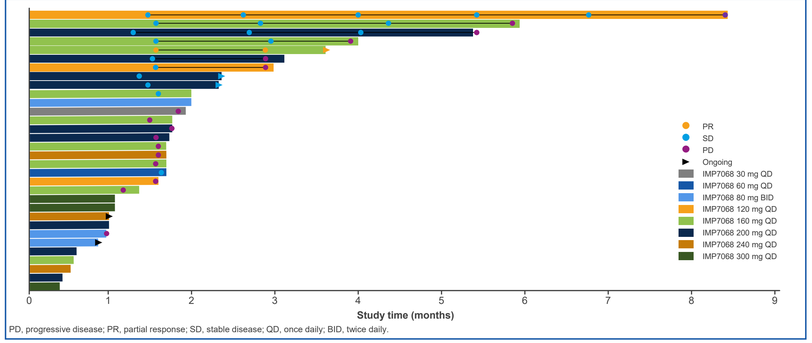


2/5, doses administered once daily for 2 days followed by 5 days off per week over each 21-day cycle; 3/4, doses administered once daily for 3 days followed by 4 days off per week over each 21-day cycle; AUC_{0-last}, area under the time–concentration curve from time 0 to the last measurable concentration of IMP7068; BID, twice daily; C_{max}, maximum plasma concentration; MD, multiple doses; SD, single dose; QD, once daily.

Preliminary efficacy

- Median treatment duration was 44 days (95% CI 30–86) and median follow-up duration was 212 days (95% CI 106 – not reached)
- 21 (65.6%) pts were evaluable for efficacy: an objective partial response was observed in one (4.8%) pt with uterine serous carcinoma
  - Ten (47.6%) pts had stable disease (SD) and ten (47.6%) experienced disease progression
- The disease control rate was 52.4%
- Among those patients with SD, four (19.0%) maintained SD for ≥12 weeks, one (4.8%) with colorectal cancer (CRC) maintained SD for >30 weeks (**Figure 4**); another pt with CRC and SD experienced a 6.7% reduction in tumor size

Figure 4: Disease response swimmer plot in all patients



PD, progressive disease; PR, partial response; SD, stable disease; QD, once daily; BID, twice daily.

Conclusions

- IMP7068 was well tolerated and conferred a WEE1-inhibitory effect, with PK and PD profiles consistent with WEE1 inhibition at each dose.
- Dose escalation including a twice-daily regimen is under evaluation to mitigate the risk of ECG QT prolonged.
- The RP2D is expected to be determined soon.
- Multiple expansion cohorts (including uterine serous carcinoma and biomarker-selected populations) will be initiated later this year.

REFERENCES

1. Bukhari AB et al. Front Oncol 2022;12:828684.
2. Zhu G et al. Front Oncol 2020;10:595187.
3. Gao A and Guo M. Biomarker Res 2020;8:44.
4. Huang L et al. Signal Transduct Target Ther 2021;6(1):386.
5. Minchom A et al. Ther Adv Med Oncol 2018;10:1–18.
6. Lin CC et al. J Clin Oncol 2022;16(suppl):e15052.

ACKNOWLEDGMENTS

The authors wish thank the study participants and all investigating teams.

PRESENTER CONFLICTS OF INTEREST

C.-C. Lin declares having received personal fees from AbbVie, Bayer, BeiGene, Blueprint Medicines, Boehringer Ingleheim, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Merck KGaA, Novartis, PharmaEngine, and Roche, outside of the presented work.

FUNDING

This study was sponsored by IMPACT Therapeutics. Medical writing and editorial support were provided by Jacqueline Kolston, PhD (Parexel) and were funded by IMPACT Therapeutics.

Corresponding author: C.-C. Lin. Email: cclin1@ntu.edu.tw