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# A Phase I Study of Safety, Pharmacokinetics, and Pharmacodynamics of SCR-6920, a Protein Arginine Methyltransferase 5 (PRMT5) Inhibitor, in Patients with Advanced Malignant Tumors

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## BACKGROUND

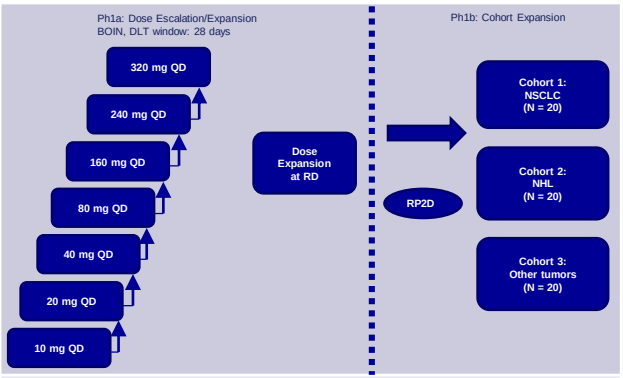
- Protein arginine methyltransferase 5 (PRMT5) catalyzes the transfer of methyl groups to the arginine residues of protein substrates including histones, spliceosomes, and transcription factors; and therefore, is involved in various biological processes[1].
- Overexpression of PRMT5 has been correlated with poor prognosis across many human cancer types[2-5]. PRMT5 plays an important role in the progression of human cancers by promoting the proliferation, invasion, and migration of cancer cells[6].
- SCR-6920, a highly potent and selective PRMT5 inhibitor, has demonstrated anti-tumor effect in multiple tumor models. SCR-6920 showed a better anti-tumor effect and lower target-related hematological toxicity than GSK3326595 in preclinical studies[7]. Evaluation of the pharmacokinetics (PK), pharmacodynamics (PD) , safety and preliminary efficacy in cancer patients is ongoing in this phase I clinical study.

## METHODS

### STUDY DESIGN

- Patients with advanced malignant tumors were enrolled in this first-in-human, multi-center open label Phase 1 study (NCT05528055). SCR-6920 was administrated orally, once daily (QD) on a 21-day cycle in tumor patients as a single agent.
- This Phase 1 study was conducted in two parts: Ph1a and Ph1b (**Figure 1**). Ph1a data are presented in this poster.
- Ph1a: Dose escalation/expansion
  - The primary objective was to evaluate the safety and tolerability and to determine the maximum tolerable dose (MTD) and the recommended phase II doses (RP2D) of SCR-6920.
  - A Bayesian Optimal Interval (BOIN) design was used to guide dose escalation with a starting dose level of 10 mg QD.
  - Cycle 0 of 7 days with only one dose administrated on day 1 was set to investigate PK profile following single-dose administration.
  - Dose-limiting toxicities (DLTs) were graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 during cycle 0 and the first 21-day treatment cycle.
  - Symmetric dimethyl arginine (SDMA), a product of PRMT5 enzymatic activity in plasma was assessed as pharmacodynamic (PD) marker.

**Figure 1. Study design**




BOIN: Bayesian Optimal Interval design; DLT: Dose Limiting Toxicity; RD: the Recommended Dose; NSCLC: non-small cell lung cancer; NHL: non Hodgkin's lymphoma; RP2D: the recommended phase II doses.

- Ph1b: Cohort expansion
  - The primary objective is to evaluate the preliminary efficacy of SCR-6920.
- NGS testing in tumor tissue was performed to investigate the relationship of efficacy with biomarker, including Methylthioadenosine phosphorylase (MTAP) and homologous recombination deficiencies (HRD) status, *etc*.

### KEY INCLUSION CRITERIA

- Histologically or cytologically confirmed diagnosis of locally advanced/metastatic solid tumors, including but not limited to non-small cell lung (NSCLC), head and neck squamous cell carcinoma (HNSCC), ovarian cancer (OC), cervical cancer, and histopathologically confirmed non-Hodgkin lymphoma.

## RESULTS

### PATIENTS

- As of 30 June 2023 (data cutoff date), twenty-five patients were enrolled and dosed from 10 to 240 mg QD during the dose escalation part (**Table 1**).
  - 64% of patients were female and median age was 51 (range, 42-71) years.
  - Tumor types in decreasing order of frequency were NSCLC (n=8, 32%), OC (n=6, 24%), cervical cancer (n=6, 24%) and other solid tumors (n=5, 20%), including liposarcoma, chondrosarcoma, gastric neuroendocrine carcinoma, colon cancer, and fallopian tube cancer (n=1 each).
  - The tumor sections from 6 patients were assessed by NGS testing, including 1 patient in 10 mg, 2 patients in 160 mg, and 3 patients in 240 mg. HRD mutation was observed in 4 patients, including 1 patient in 10 mg, 2 patients in 160 mg, and 1 patient in 240 mg. MTAP loss was not found among these 6 patients.

**Table 1:Demographic Characteristics**

| Characteristic | | 10 mg (N = 4) | 20 mg (N = 4) | 40 mg (N = 4) | 80 mg (N = 4) | 160 mg (N = 5) | 240 mg (N = 4) | Total (N = 25) |
|---|---|---|---|---|---|---|---|---|
| Age, y | median (range) | 52.5 (42 - 64) | 47.5 (43 - 67) | 52.0 (47 - 62) | 53.5 (46 - 71) | 57.0 (47 - 68) | 49.5 (44 - 66) | 51.0 (42 - 71) |
| Sex, n (%) | Male | 0 | 3 (75.0) | 3 (75.0) | 1 (25.0) | 0 | 2 (50.0) | 9 (36.0) |
| | Female | 4 (100) | 1 (25.0) | 1 (25.0) | 3 (75.0) | 5 (100) | 2 (50.0) | 16 (64.0) |
| Ethnic, n (%) | Han | 3 (75.0) | 3 (75.0) | 4 (100) | 4 (100) | 5 (100) | 4 (100) | 23 (92.0) |
| | others | 1 (25.0) | 1 (25.0) | 0 | 0 | 0 | 0 | 2 (8.0) |
| ECOG, n (%) | 0 | 0 | 2 (50.0) | 0 | 1 (25.0) | 1 (20.0) | 0 | 4 (16.0) |
| | 1 | 4 (100) | 2 (50.0) | 4 (100) | 3 (75.0) | 4 (80.0) | 4 (100) | 21 (84.0) |
| Type of cancer, n (%) | NSCLC | 1 (25.0) | 0 | 4 (100) | 1 (25.0) | 0 | 2 (50.0) | 8 (32.0) |
| | OC | 1 (25.0) | 0 | 0 | 1 (25.0) | 3 (60.0) | 1 (25.0) | 6 (24.0) |
| | Cervical cancer | 2 (50.0) | 0 | 0 | 1 (25.0) | 2 (40.0) | 1 (25.0) | 6 (24.0) |
| | Other solid tumors | 0 | 4 (100) | 0 | 1 (25.0) | 0 | 0 | 5 (20.0) |
| TNM stage, n (%) | IIIB | 0 | 0 | 0 | 0 | 0 | 1 (25.0) | 1 (4.0) |
| | IVA | 2 (50.0) | 0 | 1 (25.0) | 0 | 0 | 0 | 3 (12.0) |
| | IVB | 2 (50.0) | 0 | 3 (75.0) | 2 (50.0) | 0 | 1 (25.0) | 8 (32.0) |
| | IV | 0 | 4 (100) | 0 | 2 (50.0) | 5 (100) | 2 (50.0) | 13 (52.0) |

### SAFETY

**Dose-limiting toxicities (DLT)**

- No DLT was reported in these twenty-five patients.

**Adverse events**

- Treatment related adverse events (TRAEs) were reported in 22 (88%) patients (**Table 2**). The most common TRAEs were anemia (60%), hypoglobulinemia (32%), white blood cell count decreased (28%), neutrophil count decreased (28%), lymphocyte count decreased (20%), *etc* (**Table 3**).
- Grade ≥3 TRAEs were reported in 8 (32%) patients (**Table 2**), including anemia (n=4, 16%); lymphocyte count decreased (n=3, 12%); alanine aminotransferase increased, aspartate aminotransferase increased, and platelet count decreased (n=1, 4% each) (**Table 4**).
- Serious adverse events (SAEs) were reported in 8 (32%) patients, and SCR-6920 related SAE were reported in 4 (16%) patients (**Table 2**), which was hypoglobulinemia (n=1, 4%), colitis (n=1, 4%), anemia (n=1, 4%) and platelet count decreased (n=1, 4%) (**Table 5**).
- Overall, treatment interruptions occurred in 10 (40%) patients due to AEs (**Table 2**), including white blood cell count decreased, anemia, COVID-19, COVID-19 pneumonia, alanine aminotransferase increased, aspartate aminotransferase increased, intestinal obstruction, pyrexia, colitis, lymphocyte count decreased, extrasystoles, platelet count decreased, neutrophil count decreased. Only 1 patient discontinued treatment due to intestinal obstruction, which is not SCR-6920 related.
- Grade 5 treatment emergent adverse events (TEAEs) were reported in 2 (8%) patients and both were disease progression (PD). No Grade 5 TRAEs was reported (**Table 2**).

**Table 2. Summary of safety**

| Event, n (%) | 10 mg (N = 4) | 20 mg (N = 4) | 40 mg (N = 4) | 80 mg (N = 4) | 160 mg (N = 5) | 240 mg (N = 4) | Total (N = 25) |
|---|---|---|---|---|---|---|---|
| **TEAEs** | **4 (100)** | **3 (75.0)** | **4 (100)** | **4 (100)** | **5 (100)** | **4 (100)** | **24 (96.0)** |
| Grade ≥3 TEAEs | 3 (75.0) | 1 (25.0) | 2 (50.0) | 1 (25.0) | 3 (60.0) | 2 (50.0) | 12 (48.0) |
| **TRAEs** | **3 (75.0)** | **3 (75.0)** | **3 (75.0)** | **4 (100)** | **5 (100)** | **4 (100)** | **22 (88.0)** |
| Grade ≥3 TRAEs | 1 (25.0) | 0 | 1 (25.0) | 1 (25.0) | 3 (60.0) | 2 (50.0) | 8 (32.0) |
| **SAEs** | **1 (25.0)** | **1 (25.0)** | **1 (25.0)** | **2 (50.0)** | **2 (40.0)** | **1 (25.0)** | **8 (32.0)** |
| TR-SAEs | 0 | 0 | 1 (25.0) | 1 (25.0) | 1 (20.0) | 1 (25.0) | 4 (16.0) |
| AEs leading to dose interruption | 2 (50.0) | 1 (25.0) | 1 (25.0) | 3 (75.0) | 2 (40.0) | 1 (25.0) | 10 (40.0) |
| AEs leading to dose discontinuation | 0 | 1 (25.0) | 0 | 0 | 0 | 0 | 1 (4.0) |
| AEs leading to death | 1 (25.0) | 0 | 0 | 1 (25.0) | 0 | 0 | 2 (8.0) |

**Table 3. Treatment-related adverse events (TRAEs) occurring in ≥10% patients by PT terms**

| AEs by PT, n (%) | 10 mg (N = 4) | 20 mg (N = 4) | 40 mg (N = 4) | 80 mg (N = 4) | 160 mg (N = 5) | 240 mg (N = 4) | Total (N = 25) |
|---|---|---|---|---|---|---|---|
| Any SCR-6920 related TEAEs | 3 (75.0) | 3 (75.0) | 3 (75.0) | 4 (100) | 5 (100) | 4 (100) | 22 (88.0) |
| Anemia | 1 (25.0) | 1 (25.0) | 2 (50.0) | 3 (75.0) | 4 (80.0) | 4 (100) | 15 (60.0) |
| Hypoglobulinemia | 0 | 1 (25.0) | 2 (50.0) | 2 (50.0) | 1 (20.0) | 2 (50.0) | 8(32.0) |
| White blood cell count decreased | 1 (25.0) | 2 (50.0) | 0 | 1 (25.0) | 2 (40.0) | 1 (25.0) | 7(28.0) |
| Neutrophil count decreased | 1 (25.0) | 2 (50.0) | 0 | 1 (25.0) | 2 (40.0) | 1(25.0) | 7(28.0) |
| Lymphocyte count decreased | 0 | 0 | 1 (25.0) | 0 | 2 (40.0) | 2 (50.0) | 5 (20.0) |
| Nausea | 0 | 0 | 0 | 1 (25.0) | 2 (40.0) | 1 (25.0) | 4 (16.0) |
| Diarrhoea | 0 | 1 (25.0) | 1 (25.0) | 1 (25.0) | 1 (20.0) | 0 | 4 (16.0) |
| Decrease appetite | 0 | 0 | 1 (25.0) | 0 | 1 (20.0) | 2 (50.0) | 4 (16.0) |
| Proteinuria | 1 (25.0) | 0 | 1 (25.0) | 1 (25.0) | 0 | 0 | 3 (12.0) |
| Asthenia | 0 | 1 (25.0) | 0 | 0 | 1 (20.0) | 1 (25.0) | 3 (12.0) |
| Weight decreased | 0 | 0 | 0 | 0 | 2 (40.0) | 1 (25.0) | 3 (12.0) |
| Alopecia | 0 | 0 | 0 | 0 | 2 (40.0) | 1 (25.0) | 3 (12.0) |
| Platelet count decreased | 0 | 0 | 0 | 1 (25.0) | 0 | 2 (50.0) | 3 (12.0) |
| Protein total decreased | 0 | 1 (25.0) | 0 | 1 (25.0) | 1 (20.0) | 0 | 3 (12.0) |

**Table 4. Grade ≥ 3 TRAEs by PT terms**

| AEs by PT, n (%) | 10 mg (N = 4) | 20 mg (N = 4) | 40 mg (N = 4) | 80 mg (N = 4) | 160 mg (N = 5) | 240 mg (N = 4) | Total (N = 25) |
|---|---|---|---|---|---|---|---|
| Grade ≥ 3 TRAEs | 1 (25.0) | 0 | 1 (25.0) | 1 (25.0) | 3 (60.0) | 2 (50.0) | 8 (32.0) |
| Anemia | 0 | 0 | 0 | 1 (25.0) | 3 (60.0) | 0 | 4 (16.0) |
| Lymphocyte count decreased | 0 | 0 | 1 (25.0) | 0 | 0 | 2 (50.0) | 3 (12.0) |
| Alanine aminotransferase increased | 1 (25.0) | 0 | 0 | 0 | 0 | 0 | 1 (4.0) |
| Aspartate aminotransferase increased | 1 (25.0) | 0 | 0 | 0 | 0 | 0 | 1 (4.0) |
| Platelet count decreased | 0 | 0 | 0 | 0 | 0 | 1 (25.0) | 1 (4.0) |

**Table 5. Treatment-related serious AEs (TR-SAEs) by PT terms**

| AEs by PT, n (%) | 10 mg (N = 4) | 20 mg (N = 4) | 40 mg (N = 4) | 80 mg (N = 4) | 160 mg (N = 5) | 240 mg (N = 4) | Total (N = 25) |
|---|---|---|---|---|---|---|---|
| TR-SAEs | 0 | 0 | 1 (25.0) | 1 (25.0) | 1 (20.0) | 1 (25.0) | 4 (16.0) |
| Hypoglobulinemia | 0 | 0 | 1 (25.0) | 0 | 0 | 0 | 1 (4.0) |
| Colitis | 0 | 0 | 0 | 1 (25.0) | 0 | 0 | 1 (4.0) |
| Anemia | 0 | 0 | 0 | 0 | 1 (20.0) | 0 | 1 (4.0) |
| Platelet count decreased | 0 | 0 | 0 | 0 | 0 | 1 (25.0) | 1 (4.0) |

### PRELIMINARY EFFICACY

- Preliminary efficacy was evaluated according to RECIST 1.1. Overall, confirmed partial response (PR) was observed in one OC patient with HRD receiving 10 mg QD. And stable disease (SD) were observed in 4 patients with NSCLC, 2 patients with OC, and 1 patient with fallopian tube cancer (**Figure 2 & 3**).

**Figure 2. swimmer plot for duration of treatment**

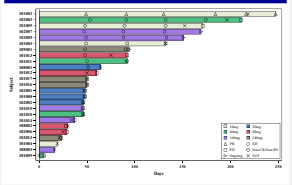
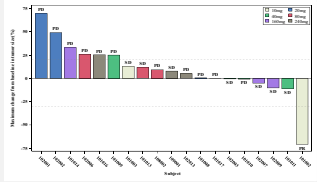


**Figure 3. waterfall plot for maximum change from baseline in Sum of Diameters for Target Lesions**



### PHARMACOKINETICS (PK) and PHARMACODYNAMICS (PD)

- Available PK (**Figure 4**) indicated fast absorption with median $T_{max}$ less than 1 hour.
- Concentration-dependent plasma-blood partition was observed (**Figure 5**), potentially leading to a non-linear PK in both plasma and blood from 10 to 160 mg QD; The terminal $t_{1/2}$ was <1 day and > 3 days in plasma and blood, respectively.
- The exposure of major metabolite SCR-6959 accounted for 30~80% compared with those from SCR-6920 across current dose levels.
- Plasma symmetric dimethyl arginine (SDMA), the enzymatic product of PRMT5 was significantly reduced (by 52.8%~82.3% compared to baseline) at steady state in dose-dependent manner (**Figure 6**).

**Figure 4. Plasma PK profile for SCR-6920 at steady state**

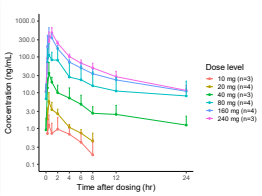



**Figure 5. Concentration-dependent plasma-blood partition in SCR-6920**

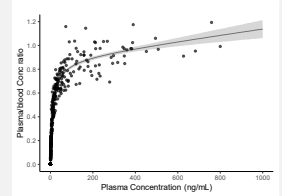
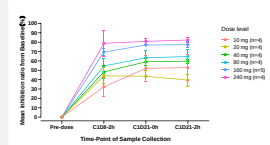



**Figure 6. SDMA inhibition in plasma relative to baseline after treatment with SCR-6920**




## CONCLUSIONS

- SCR-6920 had a manageable safety profile and further assessments are ongoing to determine the RP2Ds.
- Preliminary efficacy signal from SCR-6920 was observed in patients with NSCLC and OC.

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