Results of a phase 1 dose escalation clinical trial of NXP800, a novel GCN2 activator, in patients with advanced solid tumors

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Introduction

NXP800 is an antineoplastic, oral, small molecule activator of the GCN2 kinase. NXP800 demonstrated robust antitumor activity in preclinical models, including in ARID1a-mutated ovarian carcinoma and cholangiocarcinoma.

In a panel of human carcinoma cell lines NXP800 induced the expression of genes associated with activation of the integrated stress response (ISR). The ISR is an intracellular signal transduction network that regulates the response to various stresses; when dysregulated, it is implicated in the pathogenesis of various diseases, including cancer. Here we present data on the safety and pharmacokinetics of NXP800 from the dose escalation phase 1a trial of NXP800 in patients with advanced solid tumors.

Following this Phase 1a dose escalation study, a multicenter Phase Ib expansion in platinum-resistant ARID1a-mutated ovarian cancer has been initiated (NCT05226507) in collaboration with the GO2 Foundation and the European Network of Gynecological Oncological Trial Group (ENGOT). FDA granted Fast Track Designation to the NXP800 development program in this indication.

Material and Methods

Overall Design: A multi-center, first-in-human, open-label, dose escalation Phase 1 study in subjects with advanced solid tumors.

Primary Objective: To identify doses and dosing schedules for expansion cohorts in patients with platinum resistant, ARID1a-mutated ovarian carcinoma.

Methodology: NXP800 was administered orally once or twice a day in 28-day treatment cycles. Dose escalation was carried out according to a pre-defined sequence until a dose-limiting toxicity or a ≥ Grade 2 non-DLT toxicity at least possibly related to NXP800 was reported, at which time a modified continual reassessment method Bayesian model guided further dose escalations with the aim to recommend the next dose with estimated DLT probability closest to a target level of 30% but < 35%.

Baseline Characteristics and Exposure

Parameter N = 18
Age (years) Median (Range) 65 (42 - 77)
Sex [n, %]
Female 9 (50)
Male 9 (50)
ECOG PS (n, %)
0 4 (22)
1 13 (72)
2 1 (6)
Prior Lines of Anticancer Treatment a
Median (Range) 5 (3-12)
Duration of Exposure (days) Mean (SD) 56 (48)
Range 1 - 376
Including surgery

Common Treatment Emergent Adverse Events

Adverse Event [n, %] Grade 1 Grade 2 Grade 3 Total
Nausea 7 (39) 7 (39) 1 (6) 15 (83)
Vomiting 10 (56) 5 (28) 0 (0) 15 (83)
Diarrhea 4 (22) 5 (28) 1 (6) 10 (56)
Fatigue 2 (11) 5 (28) 0 (0) 7 (39)
Decreased appetite 3 (17) 2 (11) 0 (0) 5 (28)
ALT increase 3 (17) 1 (6) 0 (0) 4 (22)
AST increase 3 (17) 1 (6) 0 (0) 4 (22)
Thrombocytopenia 1 (6) 1 (6) 2 (11) 4 (22)
Anemia 2 (11) 1 (6) 0 (0) 3 (17)
Agranulocytosis 1 (6) 2 (11) 0 (0) 3 (17)
Dehydration 0 (0) 2 (11) 1 (6) 3 (17)
Diabetes 2 (11) 1 (6) 0 (0) 3 (17)
Weight decrease 2 (11) 1 (6) 0 (0) 3 (17)

Bayesian CRM Results

Dose Escalation (QD schedule)
50 mg 75 mg 100 mg 250 mg
Probability of DLT 0.2 0.23 0.26 0.34
Maximum tolerated Dose: 100 mg/day

Pharmacokinetics

Non-compartmental analysis
Mean T_{max} of 3.9 (50 mg/day) and 3.0 (75 mg/day) hours.
Modest accumulation following multiple doses: accumulation ratio for C_{trough} 1.3 - 2.2 and AUC_{trough} 1.6 - 3.0 (range of mean values across 50-150 mg/day, QD doses).

Population PK Modeling & Simulation
One compartment PK model estimated t_{1/2} of 12h and volume of distribution of 218L.
Based on data from clinical samples, following administration of 75 mg/day and 50 mg/day once per day the systemic exposures of NXP800 was at the level of exposure measured in a preclinical sensitive model of ARID1a-mutated ovarian carcinoma (OKVO).

References
1. Pasqua et al., “HG3 Pathway Inhibitor Clinical Candidate (CC-70144) NXP800 Developed from a Phenotypic Screen as a Potential Treatment for Refractory Ovarian Cancer and Other Malignancies,” J Med Chem, 2023

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