NuvectisPharma, Inc.

Poster Number: B044

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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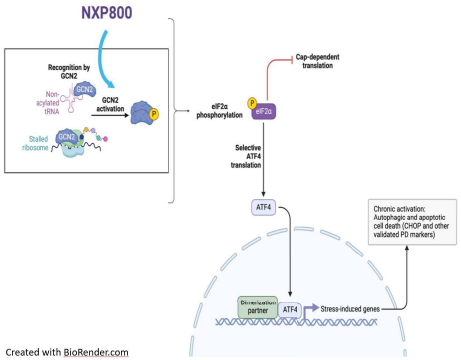
Introduction

NXP800 is an antineoplastic, oral, small molecule activator of the GCN2 kinase[1]. 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[2,3]. 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 1b expansion in platinum-resistant ARID1A-mutated ovarian cancer has been initiated (NCT05226507) in collaboration with the GOG Foundation and the European Network of Gynecological Oncological Trial Group (ENGOT). FDA granted Fast Track Designation to the NXP800 development program in this indication.

NXP800 Mechanism of Action



NXP800 causes activation of the kinase GCN2, resulting in:

- Chronic activation of the integrated stress response (ISR)
- Inhibition of cap-dependent translation

❖Chronic activation of the ISR results in cancer cell death

❖A vulnerability of ARID1a-mutated tumors is their increased dependence on translation, which is exploited by NXP800

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 < 33%.

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 (89)
Range	1 - 376

[a] Including surgery

Common Treatment Emergent Adverse Events

Adverse Event [a] (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)
AST increase	3 (17)	1 (6)	0 (0)	4 (22)
Thrombocytopenia	1 (6)	1 (6)	2 (11)	4 (22)
ALT increase	2 (11)	1 (6)	0 (0)	3 (17)
Anemia	1 (6)	2 (11)	0 (0)	3 (17)
Constipation	2 (11)	1 (6)	0 (0)	3 (17)
Dehydration	0 (0)	2 (11)	1 (6)	3 (17)
Dizziness	2 (11)	1 (6)	0 (0)	3 (17)
Weight decrease	2 (11)	1 (6)	0 (0)	3 (17)

[a] Reported in >15%; includes all subjects that took at least 1 dose of NXP800 across all doses (50-150 mg/day) and schedules (QD and BID).

Bayesian CRM Results

Dose Escalation (QD schedule)	50 mg	75 mg	100 mg	150 mg
Probability of DLT	0.2	0.23	0.26	0.34

Maximum tolerated Dose: 100 mg/day

Summary:

- 18 patients treated with NXP800, median age 65 y/o, 50% females, 72% ECOG PS=1, median of 5 prior lines of therapy.
- Most common TEAEs: nausea, vomiting, diarrhea, fatigue, decreased appetite; most common lab abnormalities: AST and ALT increase, thrombocytopenia, anemia.
- None of the most common TEAEs were > Grade 3.
- Antiemetic guidelines implemented for management of nausea/vomiting.
- Longest treatment duration: >1 year.
- MTD (QD schedule): 100 mg/day.

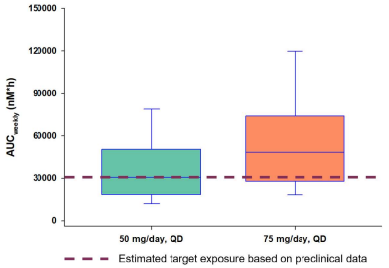
Pharmacokinetics

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_{max}: 1.3 - 2.2 and $AUC_{0\text{-}24h}$:1.6 - 3.0 (range of mean values across 50-100 mg/day, QD doses).

Population PK Modeling & Simulation

- One compartment PK model estimated $t_{1/2}$ of 13h 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 (SKOV3).



Highlights and Conclusions

- Adverse events were consistent with the preclinical toxicology data
- Maximum duration of exposure: 376 days
- MTD was determined to be 100 mg/day in a once per day dosing schedule
- Clinically relevant plasma NXP800 concentration achieved
- Evaluation of pharmacodynamic response ongoing
- **Selected regimens for Part B: 50 mg/day and 75 mg/day administered once per day**

Phase 1b - NXP800 in Platinum Resistant, ARID1a-mutated Ovarian Carcinoma

- Conducted in collaboration with GOG (GOG-3087) and ENGOT (ENGOT-GYN5/NCRI/NXP800-101) (NCT05226507)
- Key Inclusion / Exclusion criteria
  - ARID1a mutation as determined by a DNA based Next Generation Sequencing
  - disease progression within 6 months from completion of platinum-based therapy
  - Histology: ovarian clear cell and endometrioid carcinomas

References, Contacts and Acknowledgements

References

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Acknowledgments

UK investigators acknowledge infrastructural funding for clinical trials from Experimental Cancer Centre and Biomedical Research Centre initiatives.

NXP800 was discovered at The Institute of Cancer Research, Sutton, London.