A phase I study of Nelmastobart (hSTC810), an anti-BTN1A1 antibody, in patients with advanced solid tumors

Soohyeon Lee MD PhD[1], Sangjoon Shin MD PhD[2], Patricia LoRusso DO[3], Hyunjin Jung MD[4], Stephen S. Yoo PhD[4,5], and David S. Hong MD[6]

[1]Korea University Anam Hospital, Seoul, Korea, [2]Yonsei Cancer Center, Seoul, Korea, [3]Yale Cancer Center, New Haven, CT, United States, [4]STCube, Inc., Seoul, Korea, [5]STCube Pharmaceutical, Inc., Gaithersburg, MD, United States, [6]MD Anderson Cancer Center, Houston, TX, United States

ASCO Poster # 475

Background

- **Butyrophilin 1A1 (BTN1A1)**, a novel immune checkpoint protein, has been studied extensively in preclinical models to characterize its immunomodulatory functions, revealing its ability to inhibit the proliferation of activated T cells and the ability of these cells to kill tumors cells *in vitro*.
- *In vivo*, BTN1A1-overexpressing tumor models exhibit accelerated growth, whereas the growth of BTN1A1-deficient tumors is impaired in immunocompetent settings, supporting a role for this protein in the regulation of immune evasion.
- BTN1A1 exhibits **a mutually exclusive expression pattern to that of PD-1/PD-L1**, making anti-BTN1A1 antibody therapy an attractive option for cancer patients with PD-L1 refractory or relapsed disease.

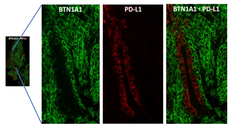

Figure 1. OPAL multiplex staining showing mutually exclusive expression between BTN1A1(green) and PD-L1(red)

Study Design

A first-in-human, multicenter, open-label, phase 1 study to investigate the safety, tolerability, pharmacokinetics, and preliminary efficacy of Nelmastobart monotherapy in patients with advanced solid tumors. (NCT05231746)

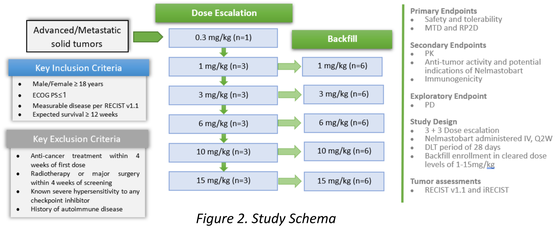

Figure 2. Study Schema

Patient Characteristics (Data cut-off: 01 May 2023)

Characteristics Statistic/Category	0.3 mg/kg (N=1)	1 mg/kg (N=10)	3 mg/kg (N=9)	6 mg/kg (N=9)	10 mg/kg (N=9)	15 mg/kg (N=6)	Total (N=44)
Country, n (%)							
KOR	1 (100.0)	9 (90.0)	6 (66.7)	7 (77.8)	7 (77.8)	5 (83.3)	35 (79.5)
USA	0 (0.0)	1 (10.0)	3 (33.3)	2 (22.2)	2 (22.2)	1 (16.7)	9 (20.5)
Age category, n (%)							
< 65 years	0 (0.0)	6 (60.0)	7 (77.8)	7 (77.8)	6 (66.7)	3 (50.0)	29 (65.9)
≥ 65 years	1 (100.0)	4 (40.0)	2 (22.2)	2 (22.2)	3 (33.3)	3 (50.0)	15 (34.1)
Sex, n (%)							
Male	1 (100.0)	5 (50.0)	5 (55.6)	5 (55.6)	3 (33.3)	4 (66.7)	23 (52.3)
Female	0 (0.0)	5 (50.0)	4 (44.4)	4 (44.4)	6 (66.7)	2 (33.3)	21 (47.7)
Primary cancer type (n, %)							
CRC	1 (100.0)	2 (20.0)	8 (88.9)	3 (33.3)	1 (11.1)	2 (33.3)	17 (38.6)
Lung	0 (0.0)	2 (20.0)	0 (0.0)	2 (22.2)	1 (11.1)	0 (0.0)	5 (11.4)
Skin	0 (0.0)	0 (0.0)	1 (11.1)	1 (11.1)	1 (11.1)	0 (0.0)	3 (6.8)
Ovary	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (11.1)	1 (16.7)	3 (6.8)
Biliary tract	0 (0.0)	1 (10.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	2 (4.5)
Bladder	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	2 (4.5)
Breast	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	2 (4.5)
Pancreas	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.5)
Adrenocortical carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (2.3)
Esophagus	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)
Head and neck	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)
PEComa	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (2.3)
Thymic cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (2.3)
Ureter	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (2.3)
Duodenal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (2.3)
Peritoneal mesothelioma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (2.3)
Previous lines of systemic anticancer therapy, n (%)							
1	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	2 (4.5)
2	1 (100.0)	2 (20.0)	0 (0.0)	3 (33.3)	1 (11.1)	2 (33.3)	9 (20.5)
3	0 (0.0)	2 (20.0)	2 (22.2)	4 (44.4)	2 (22.2)	2 (33.3)	12 (27.3)
≥ 4	0 (0.0)	5 (50.0)	7 (77.8)	2 (22.2)	6 (66.7)	1 (16.7)	21 (47.7)

Table 1. Baseline Demographics

Study Results (Data cut-off: 31 Jan 2023)

Safety

Nelmastobart is safe and well-tolerated:

- No AEs that met DLT criteria across all dose levels
- No AEs that were dose-related or time-related
- No AEs > Grade 3 considered to be related, probably related, or possibly related to Nelmastobart
- Most common AEs: Grade 1 or 2 fatigue, headache, nausea, somnolence

	0.3 mg/kg (N=1)	1 mg/kg (N=10)	3 mg/kg (N=8)	6 mg/kg (N=9)	10 mg/kg (N=8)	15 mg/kg (N=3)	Total (N=39)
Any AEs, n(%)	1 (100.0)	10 (100.0)	8 (100.0)	9 (100.0)	4 (50.0)	0 (0.0)	32 (82.1)
TEAEs, n(%)							
Any TEAEs	1 (100.00)	10 (100.0)	8 (100.0)	9 (100.0)	4 (50.0)	0 (0.0)	32 (82.1)
TESAEs	0 (0.0)	4 (40.0)	1 (12.5)	2 (22.2)	2 (25.0)	0 (0.0)	9 (23.1)
CTCAE Grade 3/4/5 TEAEs	0 (0.0)	3 (30.0)	2 (25.0)	2 (22.2)	1 (12.5)	0 (0.0)	8 (20.5)
Study drug-related, n(%)							
Any TEAEs	0 (0.0)	4 (40.0)	6 (75.0)	5 (55.6)	3 (37.5)	0 (0.0)	18 (46.2)
Any TESAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CTCAE Grade 3/4/5 TESAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 2. Summary of Adverse Events by Cohort

Figure 3. Most Common Adverse Events

Efficacy (Data cut-off: 01 May 2023)

- Nelmastobart shows durable PFS in patients with a variety of tumor types
- Best overall response of 1 PR, 16 SD, and 3 MXR
- Duration of participation for each patient is approximately 66 weeks (Study duration includes screening, treatment, and safety follow-up period)

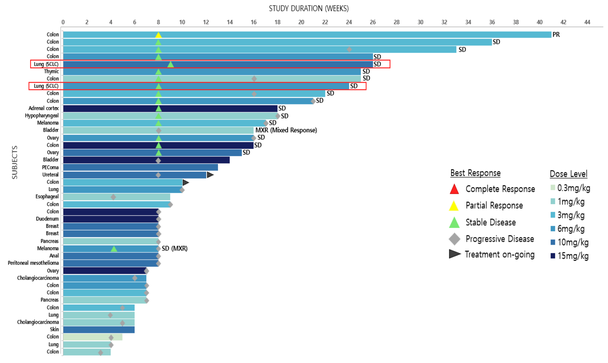

Figure 4. Swimmers Plot of Best Overall Response

Pharmacokinetics & Anti-drug Antibodies

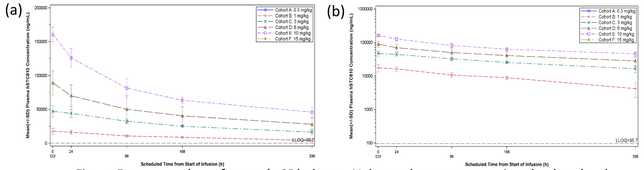

Figure 5. present plots of mean (±SD) plasma Nelmastobart concentrations by dose level on (a) linear and (b) semi-logarithmic scales, respectively, for the PK Population in Cycle 1.

- In Cycle 1, the mean maximum plasma concentrations generally increased with the increasing dose of each cohort. Across all cohorts, plasma concentrations gradually declined, with measurable concentrations seen at 336 hours post-dose.
- The estimated slopes of the dose versus exposure relationships (with 90% CIs) were 0.8915 (0.8203, 0.9628) for Cmax and 0.8879 (0.7465, 1.0292) for AUC0-14d,ss across 1 mg/kg (Cohort B) and 10 mg/kg (Cohort E) cohorts. The dose proportionality was not considered established for Cmax across 1 mg/kg (Cohort B) and 10 mg/kg (Cohort E) cohorts since the 90% CIs of the estimated slopes did not include the value of 1. Dose proportionality was observed for AUC0-14d,ss across 1 mg/kg (Cohort B) and 10 mg/kg (Cohort E) cohorts based on Hummel criteria but was not observed based on Smith criteria.
- Overall, Cmax and AUC0-14d were generally similar among ADA-positive and ADA-negative patients in the study, and across all cohorts, for Cycle 1 and Cycle 5.

Notable Patients

Colorectal Cancer

- 62 y/o M, **MSI-H CRC** with lung, lymph node metastases
- 3 prior chemotherapy regimens
- Biomarkers: ↑ TNF-α, $CD14^+$ monocytes; ↓$CD4^+CD25^+$ cells
- 3 mg/kg Nelmastobart: **Partial Response**
- **PFS = 10 months ↑**

Small Cell Lung Cancer

- 75 y/o M, ES-SCLC
- Progressed on durvalumab + tremelimumab clinical trial
- Biomarkers: ↑IFN-γ, $CD8^+CD25^+$ cells;↓MCP-1
- 10 mg/kg Nelmastobart: Stable Disease
- **PFS = 6 months ↑**

Small Cell Lung Cancer

- 72 y/o M, ES-SCLC
- Progressed on EP + pembrolizumab + olaparib clinical trial
- Biomarkers: ↑ IFN-γ, $CD8^+CD25^+$ cells; ↓$CD4^+CD25^+$ cells
- 6 mg/kg Nelmastobart: Stable Disease
- **PFS = 5.5 months ↑**

Patient with Post-treatment Response

Colorectal Cancer

- 75 y/o M, MSS CRC with liver metastasis
- 2 prior chemotherapy regimens
- Biomarkers: ↑ IFN-γ, TNF-α, $CD8^+CD25^+$ cells; ↓$CD4^+CD25^+$ cells
- 0.3 mg/kg Nelmastobart: Progressive Disease
- **Post-treatment scan after 4 cycles of capecitabine showed PR**

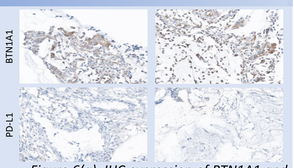

Figure 6(a). IHC expression of BTN1A1 and PD-L1 in MSI-H CRC

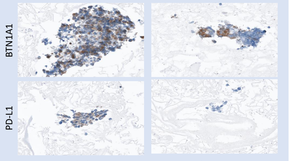

Figure 6(b). IHC expression of BTN1A1 and PD-L1 in 6 mg/kg SCLC

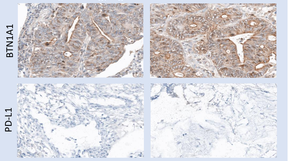

Figure 6(c). IHC expression of BTN1A1 and PD-L1 in MSS CRC

Cytokines

- Overall, there were no major cytokine changes and no cytokine-related toxicities after initiation of Nelmastobart.
- An upward trend is observed in IFN-γ and IL-6 with individual fluctuations in TNF-α and MCP-1.
- Further analysis is required to observe any correlations with Nelmastobart.

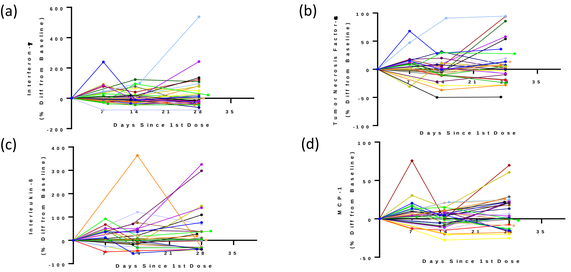

Figure 7(a) – (d). Cytokine panel changes after initiation of Nelmastobart

Immunophenotype

- Overall, a downward trend was observed in $CD4^+CD25^+$ T cells with individual fluctuations in other cell phenotypes.
- Further analysis is required to observe any correlations with Nelmastobart.

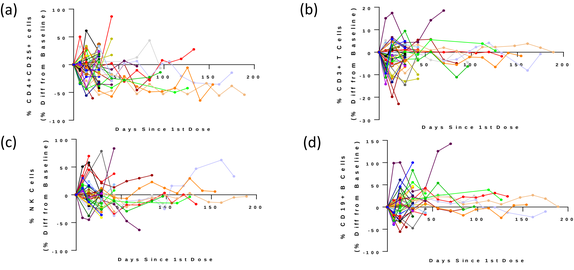

Figure 8(a) – (d). Immunophenotype changes after initiation of Nelmastobart

Conclusion

- The findings from this interim analysis indicate that plasma concentrations of Nelmastobart are stable showing gradual increase with increasing dose administered and gradually decrease over time.
- Nelmastobart has a highly tolerable safety profile. There are no DLTs across all dose levels and MTD is not reached. There are no TESAEs, CTCAE grade 3/4/5 TEAEs, or deaths related to Nelmastobart.
- Although a heavily pre-treated and heterogenous patient population was enrolled, Nelmastobart demonstrated encouraging anti-tumor activity. Notably, in comparison to the historical PFS of 2-4 months seen in ES-SCLC patients, SCLC patients on Nelmastobart are currently showing a PFS of 6+ months with treatment still ongoing
- A multi-national phase 1b/2 study is planned in relapsed or refractory small cell lung cancer and other tumor types.
- The RP2D dose for further clinical development will be selected after additional analysis.