Phase I Safety and Pharmacokinetic Study of KN035, the first subcutaneously administered, novel fusion Anti-PD-L1 Antibody in Japanese Patients with Advanced Solid Tumors

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Background

- KN035 is a novel fusion protein of humanized anti-PD-L1 single domain antibody and human IgG1 Fc, formulated for subcutaneous (SC) injection.
- A phase I safety and pharmacokinetic (PK) study was conducted in Japan to evaluate the safety and tolerability, PK, immunogenicity, and antitumor activity of KN035 in Japanese patients with previously treated advanced solid tumors.

Objective and Study Population

- Primary objective: To evaluate and characterize the tolerability and safety profile of single agent KN035 in adult subjects with unresectable advanced carcinoma.
- Secondary objective: To characterize the PK profile, determine maximum tolerated dose (MTD) and to evaluate the antitumor activity of single agent KN035.

Key Eligibility Criteria:

- Histological or cytological confirmed advanced carcinoma, who had failed standard therapies, been intolerant to such therapy or considered ineligible for standard therapy
- Eastern cooperation oncology group performance scale (ECOG) 0-1.
- Adequate hematologic and organ function.
- Active autoimmune disease, pneumonitis were excluded. Patients who had prior treatment with PD-L1 are excluded.

Method

- Patients with advanced solid tumors were treated with KN035 SC once every-7-days (QW) or once every-14-days (Q2W) schedules with the dose limiting toxicities (DLT) evaluation period of 28 days.
- For the QW schedule, traditional 3+3 design was adopted and three dose levels of 1 mg/kg(n=3) , 2.5 mg/kg (n=4)and 5 mg/kg (n=3) were planned. For the Q2W schedule, 6 patients were planned at each dose levels of 2.5 and 5 mg/kg.
- Adverse events (AEs) were assessed using CTCAE v4.0, and tumor response was assessed using RECIST v1.1 every 12 weeks.
- Full PK sampling was performed after the first dose of cycle 1 (28 days) and sparse PK samples were collected at pre-dose and around C_{max} during the subsequent Cycles.

Results

As of 5 May 2019,a total of 26 patients have been enrolled. Patient baseline demographic and disease characteristic are summarized in Table 1. At the time of data cut-off, 3 patients were still on treatment, 21 patients discontinued treatment due to disease progression and 2 patients discontinued treatment due to adverse events. No DLT was reported. Only One patient in 5mg/kg, Q2W cohort experienced a drug related grade 3 AE (cerebral infarction) as show in Table 2.

Pharmacokinetics Results

- In the escalation phase, the exposure to KN035 is dose-dependent and increase proportionally and T_{max} varied from 96 to 168 hours after single dose as shown in Figure 1.
- In the expansion phase, the exposure to KN035 is dose-dependent and increase proportionally and T_{max} varied from 96 to 120 hours after single dose as shown in Figure 2.
- Preliminary PK suggested a prolonged half life that would support a less frequent dosing schedule.

Figure 1: Pharmacokinetics (Escalation Part)

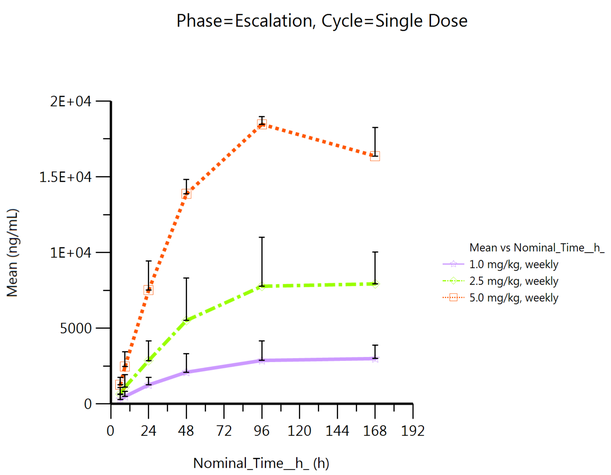


Figure 2 : Pharmacokinetics (Expansion Part)

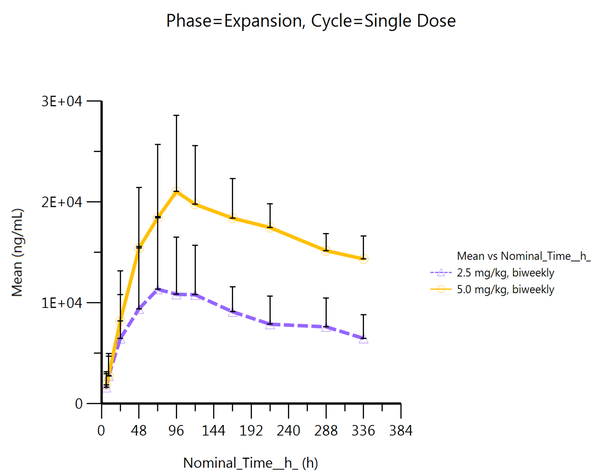


Table 1: Baseline Characteristics

Characteristic	Overall (n=26)	Cancer diagnosis, n(%)	
Median Age (years)(range)	59(35-78)	Cholangiocarcinoma	3(11.5)
Males, N(%)	11, (42)	Urotherial carcinoma	2(7.6)
ECOG		Ovarian cancer	2(7.6)
0	12(46)	Colon cancer	2(7.6)
1	14(54)	Pancreatic cancer	2(7.6)
Number of Prior systemic treatment		Leiomyosarcoma	2(7.6)
1	2(7.6)	Others	13(50)
2	4(15)		
3-5	12(46)		

Table 2: Summary of Adverse Events

Number of patients(%)	Total Number (N=26) (%)	1.0 mg/kg, Weekly (N=3) (%)	2.5mg/kg ,weekly (N=4)(%)	5.0mg/kg Weekly, (N=3)(%)	5.0mg/Q2W (N=9)(%)	2.5mg/Q2W (N=7)(%)
Any AE	23(88)	3(100)	4(100)	3(100)	7(78)	5(71)
Related AE	17(65)	3(100)	3(75)	1(33)	6(67)	3(43)
Grade 3-4 AE	7(27)	0(0)	2(50)	1(33)	2(22)	2(28)
Related Grade 3-4 AE	1(4)	0(0)	0(0)	0(0)	1(11)	0(0)
Grade 5 AE	1(4)	0(0)	1(25)	0(0)	0(0)	0(0)
Related Grade 5 AE	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Any SAE	4(15)	0(0)	2(50)	0(0)	1(11)	1(14)
Related SAE	2(7)	0(0)	0(0)	0(0)	1(11)	1(14)

Clinical Efficacy

Reduction in target lesions by investigator assessment is summarized in Figure 3. As of 5 May 2019, 26 pts have been enrolled, of which 9 pts completed at least one on-study assessment (every 3 months). Two pts had confirmed PR, including one esophageal cancer pt at 5mg/kg biweekly cohort (treatment response duration 9 months) and one urothelium carcinoma pt at 0.3mg/kg weekly cohort (treatment duration 13 months). Two additional pts had unconfirmed PR and 5 pts achieved SD. One pt had only non-target lesion at baseline is not shown in Figure 3. A case with partial response is shown in Figure 4.

Figure 3: The Best Responses of Target Lesions

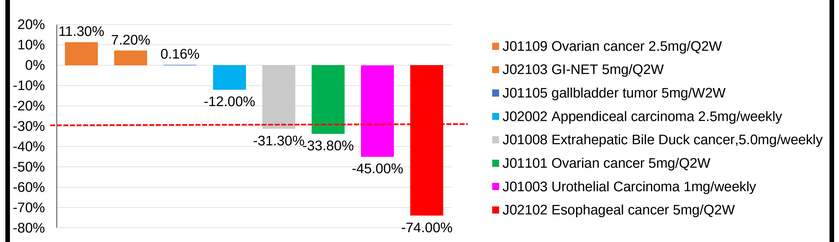
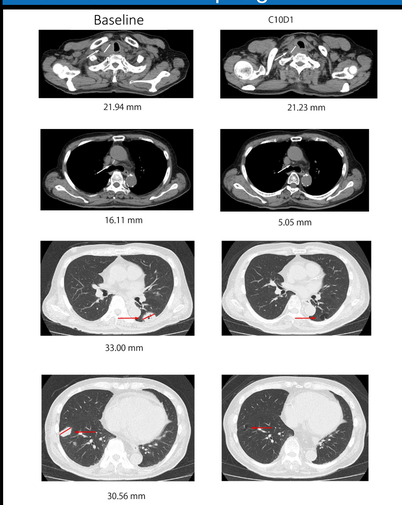


Figure 4: PR Observed in Patient J02102 with Esophageal Cancer



Conclusion

- KN035 exhibits a tolerable safety profile in patients with advanced malignancies and preliminary results demonstrated encouraging anti-tumor activity.
- Based on PK data from the Q2W schedule, a fixed dose with less frequent dosing schedule of every 4 weeks is presently being evaluated.

ClinicalTrials.gov Identifier: NCT03248843. For questions related to this poster, please contact lead author Toshio Shimizu (tosshimi@ncc.go.jp)

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