Summary of Phase 1a Dose Escalation Clinical Study Data for Dual Angiogenic Bispecific Antibody Targeting VEGF and DLL4 (ABL001/NOV1501/TR009) in Patients with Previously Treated Solid Tumors

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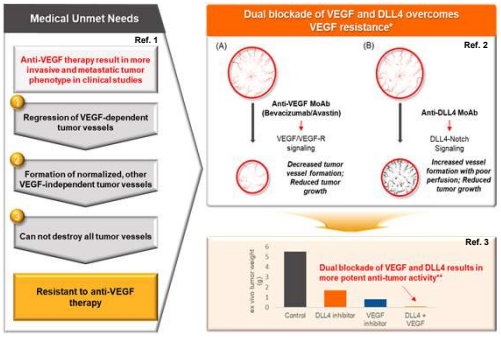
Abstract

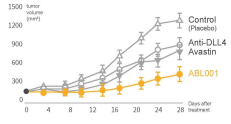
Emerging reports suggest Delta-like-ligand 4 (DLL4) is a promising target to augment the effects of VEGF inhibitors. Simultaneous blockade of VEGF/VEGFR and DLL4/Notch signaling pathways leads to more potent inhibition of tumor progression by a synergistic anti-angiogenic mechanism in various mouse xenograft models. We have developed a bispecific antibody targeting VEGF and DLL4 (ABL001/NOV1501/TR009) showing more potent in vivo biological activity as compared to respective VEGF-targeting or DLL4-targeting monoclonal antibodies. Currently the safety and tolerability of ABL001 is being evaluated in a phase 1A dose escalation study (ClinicalTrials.gov Identifier: NCT03292783). To be eligible for the study, patients must have progressed due to toxicity or lack of response to all standard available treatments including traditional chemotherapies, targeted biological drugs and tyrosine kinase inhibitors (multi-VEGF/ VEGF-R2, anti-HER2, anti-EGFR, etc.) and immunotherapies (anti-PD-1), where relevant. The study is designed in a classical 3+3 dose-escalation schema where ABL001 is administered by IV across 9 dose cohorts ranging from 0.3, 1, 2.5, 5, 7.5, 10, 12.5, 15 and 17.5 mg/kg biweekly. Patients in each cohort were examined for DLT (dose limiting toxicity) for 3 weeks after the first administration of ABL001. Tumor assessments (CT scans) were performed every 6 weeks and cardiac assessments were performed every cycle. No DLT was observed during the 7-cohort dose escalation phase and the maximum tolerated dose (MTD) has not been reached. The most common treatment-related adverse events (AEs) (including all dose levels and all grades) were hypertension, anemia, anorexia, general weakness, and headache. The clinical benefit ratio including patients with stable disease (SD) and partial response (PR) is 71.4% across all patients treated with a mean treatment duration of 3.88 months. The CBR for gastric patients was 88% with mean treatment duration of 4 months while the CBR for colorectal patients was 67% with mean duration of treatment of 7.25 months (not including 3 patients whose treatment is ongoing). Preliminary results of pharmacokinetic (PK) analysis demonstrated a slightly shorter mean half-life (9~10 days) than conventional monoclonal antibody therapeutics due to the bispecific nature of ABL001. In addition, preliminary pharmacodynamic (PD) biomarker analysis using the patients' plasma samples showed engagement of the VEGF/VEGFR and the DLL4/Notch1 pathway modulation after ABL001 administration. In summary, ABL001 is being developed as a promising therapeutic bispecific antibody for cancer treatment which seems to overcome primary anti-VEGF resistance in heavily pre-treated metastatic cancer patients. A phase 1B/2A study is planned to expand the single agent activity of ABL001 and a phase 1B combination study is planned to test ABL001 in combination with chemotherapy and/or PD-1/PD-L1 blockade therapy.

Background & Rationale

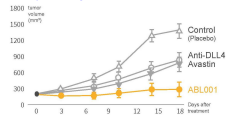


ABL001 showed better efficacy compared to Avastin or anti-DLL4 monotherapy (Ref. 4)

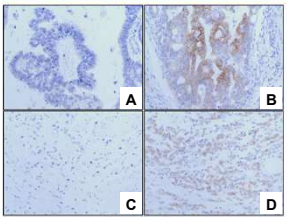
➢ Efficacy in A549 lung cancer model

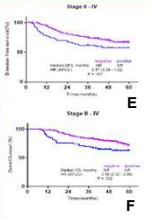


➢ Efficacy in SCH gastric cancer model



Clinical Importance & Study Design





DLL4 overexpression correlates with poor clinical outcome in gastric cancer patients. Representative microphotographs of DLL4 immunohistochemistry: (A) negative in intestinal-type, (B) positive in intestinal-type (C) negative in diffuse-type and (D) positive in diffuse-type gastric adenocarcinomas. Kaplan–Meier survival analysis based on clinical stages of gastric cancer patients: (E) DFS in stage II–IV GC, (F) OS in stage II–IV GC (Ref. 5).

❖ **Study design:**
A classical 3+3 dose-escalation schema where ABL001 is administered by IV across 9 dose cohorts ranging from 0.3, 1, 2.5, 5, 7.5, 10, 12.5, 15, and 17.5 mg/kg biweekly

❖ **Primary Objective:**
- Safety/tolerability/toxicity
- PK
- MTD (Maximum Tolerated Dose)

❖ **Secondary Objective:**
- Anti-tumor efficacy
- Immunogenicity

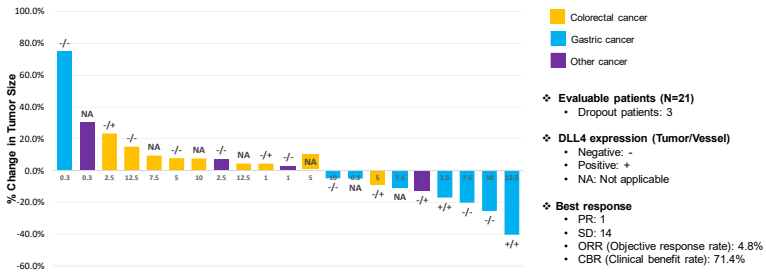
❖ **Exploratory Objective:**
- PK/PD relationship: ABL001 concentration with VEGF and Notch signaling molecules
  - ✓ Changes of plasma biomarkers
  - ✓ Changes of gene expression in PBMC
- DLL4 expression in tumor tissues: correlation with ABL001 response?

Patient Information

Clinical Characteristics	No. of Patients (N=24)
Age (years)	
Median (Range)	54 (35-81)
ECOG performance Status	
0	2
1	22
Sex	
Male	15
Female	9
Primary malignancy	
Colorectal	11
Gastric (or Gastric Esophageal)	9
Ovary	1
GIST (small intestine)	1
Cholangiocarcinoma	1
Malignant Melanoma	1

Clinical Characteristics	No. of Patients (N=24)
Previous therapy	
Chemotherapy	24
Radiotherapy	11
VEGF-targeting agents (anti-ligand, TKI)	19
Immunotherapy	8
Investigational agent	5
No. of Line of Previous Chemotherapy	
All (N=24)	Median: 4.0 (1-7)
Colorectal Cancer (N=11)	Median: 4.0 (2-5)
Gastric Cancer (N=9)	Median: 3.0 (1-5)
Others (Cholangiocarcinoma, GIST, Melanoma, Ovarian) (N=4)	Median: 4.5 (2-7)

Waterfall Plot of ABL001 Efficacy

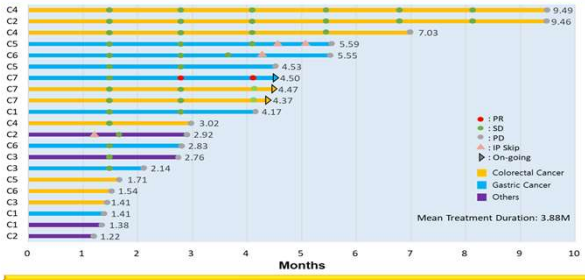


❖ **Evaluable patients (N=21)**
- Dropout patients: 3

❖ **DLL4 expression (Tumor/Vessel)**
- Negative: -
- Positive: +
- NA: Not applicable

❖ **Best response**
- PR: 1
- SD: 14
- ORR (Objective response rate): 4.8%
- CBR (Clinical benefit rate): 71.4%

Swimmer Plot of ABL001 Treatment Duration



❖ **Mean treatment duration of colorectal cancer patients (N=9): 4.31**

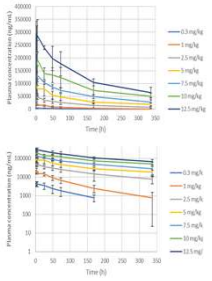
❖ **Mean treatment duration of gastric cancer patients (N=8): 3.86**

Summary of Adverse Events

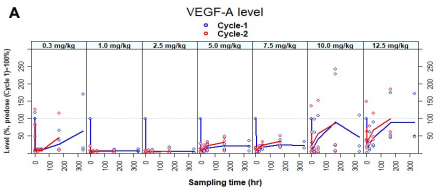
Adverse events	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Hypertension	8	9.4	9	10.6	4	4.7	0	0.0	0	0.0	21	24.7
Anemia	0	0.0	6	7.1	2	2.4	0	0.0	0	0.0	8	9.4
Aspartate Aminotransferase (AST) Increased	1	1.2	0	0.0	2	2.4	0	0.0	0	0.0	3	3.5
Epigastric Pain	1	1.2	2	2.4	0	0.0	0	0.0	0	0.0	3	3.5
General Weakness	0	0.0	2	2.4	1	1.2	0	0.0	0	0.0	3	3.5
Hypoalbuminemia	1	1.2	2	2.4	0	0.0	0	0.0	0	0.0	3	3.5
Constipation	2	2.4	1	1.2	0	0.0	0	0.0	0	0.0	3	3.5
Abdominal Pain	0	0.0	2	2.4	0	0.0	0	0.0	0	0.0	2	2.4
Alanine Aminotransferase (ALT) Increased	0	0.0	1	1.2	1	1.2	0	0.0	0	0.0	2	2.4
Alkaline Phosphatase (ALP) Increased	0	0.0	0	0.0	2	2.4	0	0.0	0	0.0	2	2.4
Anorexia	1	1.2	1	1.2	0	0.0	0	0.0	0	0.0	2	2.4
Headache	0	0.0	2	2.4	0	0.0	0	0.0	0	0.0	2	2.4
Insomnia	0	0.0	2	2.4	0	0.0	0	0.0	0	0.0	2	2.4
Malignant Neoplasm Progress	0	0.0	1	1.2	0	0.0	0	0.0	1	1.2	2	2.4
Upper Respiratory Infection	1	1.2	1	1.2	0	0.0	0	0.0	0	0.0	2	2.4

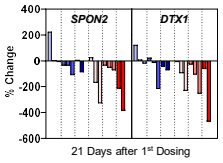
PK Profile of ABL001

PK Parameters	ABL001 (Mean ± SD)						
	Cohort 1 (0.3 mg/kg) N = 4	Cohort 2 (1 mg/kg) N = 3	Cohort 3 (2.5 mg/kg) N = 3	Cohort 4 (5 mg/kg) N = 4	Cohort 5 (7.5 mg/kg) N = 3	Cohort 6 (10 mg/kg) N = 3	Cohort 7 (12.5 mg/kg) N = 3
C_{max} (μg/mL)	4.55 ± 1.24	22.75 ± 6.69	51.21 ± 11.33	95.40 ± 20.60	139.26 ± 31.80	210.60 ± 57.01	315.56 ± 57.42
AUC_{last} (h*μg/mL)	265.86 ± 74.74	1538.58 ± 422.97	6093.03 ± 2434.91	11095.66 ± 4512.27	19200.89 ± 3377.26	29716.31 ± 6577.95	45589.18 ± 8435.03
AUC_{inf} (h*μg/mL)	378.48 ± 168.99	1633.26 ± 527.71	7742.77 ± 364 8.61	15736.68 ± 5694.04	27572.49 ± 11811.61	48584.28 ± 13474.46	64963.74 ± 14864.71
T_{max} (hr)†	2.26 (1.58 – 4.87)	1.57 (1.47 – 2.83)	1.42 (1.00 – 5.08)	2.16 (1.23 – 3.43)	1.42 (1.03 – 4.83)	1.58 (1.10 – 5.02)	1.42 (1.40 - 4.90)
$t_{1/2}$ (hr)	56.09 ± 18.83	75.64 ± 18.48	132.87 ± 49.21	165.23 ± 41.45	178.65 ± 80.88	218.50 ± 54.98	205.96 ± 31.49
CL (mL/hr/kg)	0.93 ± 0.45	0.65 ± 0.18	0.38 ± 0.19	0.35 ± 0.13	0.30 ± 0.11	0.23 ± 0.07	0.20 ± 0.05
MRT	79.54 ± 26.33	94.36 ± 30.00	187.27 ± 61.84	225.89 ± 54.44	251.53 ± 122.90	307.78 ± 70.28	282.66 ± 40.78



Summarized Results of PD/Biomarker Studies





Preliminary pharmacodynamic (PD) biomarker analysis using the patients' plasma samples showed engagement of the VEGF/VEGFR and the DLL4/Notch1 pathway modulation.
After ABL001 administration, VEGF-A level (A) and soluble Notch-1 level (B) in patient plasma were rapidly dropped. Plasma biomarkers were measured by MSD analysis and ELISA, respectively. In addition, *SPON2* and *DTX1* genes (Notch-signaling related genes, C) were decreased in most patients, which were evaluated by qRT-PCR analysis. Although the preliminary PD studies were performed with limited number of patient samples, the results demonstrated ABL001 treatment modulates VEGF and Notch signaling pathway in patients.

Conclusion & References

A bispecific antibody, ABL001 (NOV1501/TR009, previous code name: HD105)

- has been well tolerated up to 12.5 mg/kg (no significant treatment related adverse events up to 12.5 mg/kg).
- treatment-related adverse events (AEs) (including all dose levels and all grades) were hypertension, anemia, anorexia, general weakness, and headache.
- treatment showed preliminary anti-tumor activity in heavily pre-treated cancer patients [the clinical benefit ratio is 71.4% including 14 patients with stable disease (SD) and 1 patient with partial response (PR)].
- of the SD + PR patients, mean treatment durations for gastric and colorectal cohorts are 4 months and 7 months, respectively. 88% of gastric patients had prior VEGF-R2/PD-1/HER2 therapy and 100% of colorectal patients had prior VEGF/EGFR/PD1 therapy.
- pharmacokinetic (PK) analysis demonstrated a slightly shorter mean half-life (9~10 days) and preliminary pharmacodynamic (PD) biomarker analysis showed engagement of the VEGF/VEGFR and the DLL4/Notch1 pathway modulation after ABL001 administration.
- phase 1b/2a study is planned in combination of ABL001 with chemotherapy or anti-PD-1 antibody.

References

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