**Abstract #267659**

**Poster #3023**

# Phase 1a study results investigating the safety and preliminary efficacy of ABL001 (NOV1501), a bispecific antibody targeting VEGF and DLL4 in metastatic gastrointestinal (GI) cancer.

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## Abstract

**Background:** Antiangiogenic therapy has been a successful clinical strategy for the treatment of various cancer types. To date, all approved antiangiogenic drugs primarily inhibit the VEGF/VEGFR pathway. Delta-like ligand 4 (DLL4) has been identified as a potential drug target in VEGF-independent angiogenesis. A dual blockade of both VEGF and DLL4 could be a promising strategy to overcome anti-VEGF therapy resistance. ABL001 (NOV1501)* has been developed as a bispecific antibody to bind and inhibit both DLL4 and VEGF thereby significantly suppressing tumor angiogenesis.

**Methods:** In a classical 3+3 dose-escalation design, ABL001 was administered IV at doses ranging from 0.3, 1, 2.5, 5, and 7.5 mg/kg biweekly (NCT03292783: the next doses of ABL001 are 10 and 12.5 mg/kg). After the first administration of ABL001 in each cohort, DLT (dose limiting toxicity) was observed for 3 weeks. Tumor assessments were performed every 6 weeks and cardiac assessments were performed every cycle.

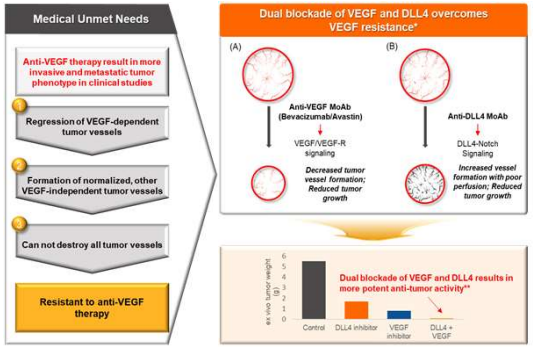
**Results:** From 2017 November to February 2019, 18 patients were enrolled on this trial. All patients were heavily pre-treated** with at least 3 prior lines of chemotherapy. All patients in cohort 4 and 5 were either metastatic colorectal cancer or gastric cancer. Of the 5 cohorts, there was no DLT observed during dose escalation. In addition, there was no maximum tolerated dose identified up to 7.5 mg/kg dose. The most common treatment-related adverse events (AEs)*** (including all dose levels and all grades) occurred were hypertension, anemia, anorexia, general weakness, nausea, and vomiting. Preliminary results of pharmacokinetic (PK) analysis demonstrated slightly shorter mean half-life than conventional monoclonal antibodies due to the bispecific nature of the ABL001. In addition, preliminary pharmacodynamic (PD) biomarker analysis using PBMC and plasma samples showed engagement of both VEGF/VEGFR and DLL4/Notch1 pathway modulation after ABL001 administration. One gastric cancer patient at 7.5 mg/kg achieved unconfirmed partial response at the time of this writing.

*TR009 (TRIGR code name), HD105 (previous code name)

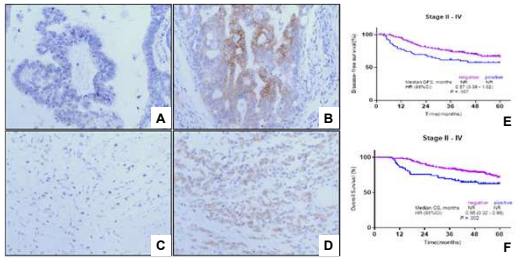
**At least 3 lines or prior chemotherapy and biological targeted agents including anti-VEGF and anti-VEGFR-2, anti-PD-1 and anti-EGFR regimens

***Based on publicly available data, the DLL4 epitopes targeted by ABL001 are distinct to DLL4 epitopes targeted by other mAbs and bsAbs

## Rationale



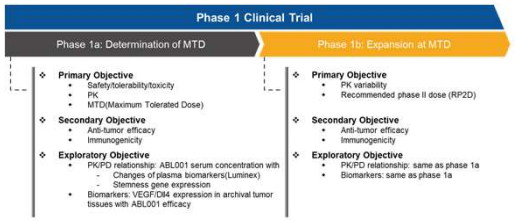

## Clinical Importance




**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.

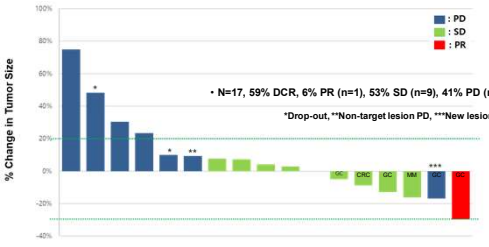
## Study Overview



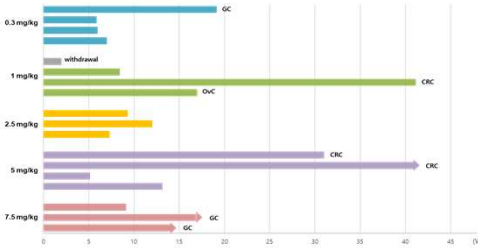

## Patient Status

| Cohort | Enrolled | D/O | DLT | Ongoing | Completed |
|---|---|---|---|---|---|
| 1 (0.3 mg/kg) | 4 | 1 | 0 | 0 | 3 |
| 2 (1.0 mg/kg) | 4 | 1 | 0 | 0 | 3 |
| 3 (2.5 mg/kg) | 3 | 0 | 0 | 0 | 3 |
| 4 (5.0 mg/kg) | 4 | 1 | 0 | 1 | 2 |
| 5 (7.5 mg/kg) | 3 | 0 | 0 | 2 | 1 |
| **Total** | **18** | **3** | **0** | **3** | **12** |

## Clinical Responses




- Waterfall plot shows changes of tumor size using minimum sums of the largest diameters of target lesions
- GC: Gastric Cancer, CRC: Colorectal Cancer, MM: Malignant Melanoma (data of withdrawal was not included)



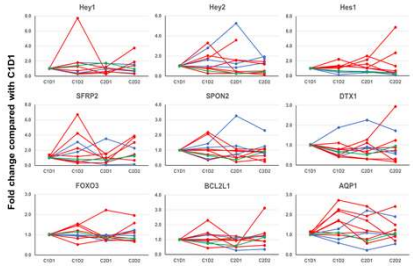

- GC: Gastric Cancer, CRC: Colorectal Cancer, OvC: Ovarian Cancer
- Treatment duration (mean): 15.5 weeks (data of withdrawal was not included)

## Adverse Events

- The total number of adverse events: 59 cases (G1: 16 cases / 27.1%, G2: 32 cases / 54.2%, ≥G3: 11 cases / 18.6%)
- Hypertension (50%; 9 pts), anemia (17%; 3 pts), hypoalbuminemia (11%; 2 pts), anorexia (11%), epigastric pain (11%), general weakness (11%), upper respiratory infection (11%)
- Hypertension: 16 cases/total 59 cases (27.1%) (G1~2: 14 cases/, G3: 2 cases), but manageable
- No drug-related pulmonary hypertension, gastric perforation or cardiac disorder seen at 7.5 mg/kg

| Event category SOC of CTCAE v4.03 | AE term | All grades Nr of subjects with at least one event n (% of total #59) | | Grade 3-4 Nr of subjects with at least one event n (% of total #59) | |
|---|---|---|---|---|---|
| | | All | Related | All | Related |
| Vascular disorders | Hypertension | 16 (27.1) | 11 | 2 (3.4) | 2 |
| Blood and lymphatic system disorders | Anemia | 8 (13.6) | 3 | 2 (3.4) | 1 |
| Metabolism and nutrition disorders | Hypoalbuminemia | 3 (5.1) | 0 | 0 | 0 |
| Gastrointestinal disorders | Abdominal pain | 2 (3.4) | 1 | 0 | 0 |
| Metabolism and nutrition disorders | Anorexia | 2 (3.4) | 1 | 0 | 0 |
| Gastrointestinal disorders | Epigastric pain | 2 (3.4) | 2 | 0 | 0 |
| General disorders and administration site conditions | General weakness | 2 (3.4) | 0 | 1 (1.7) | 0 |
| Infections and infestations | Upper respiratory infection | 2 (3.4) | 0 | 0 | 0 |

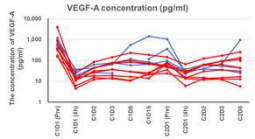
## Preliminary PD Assay Results




**Gene expression profile by qRT-PCR analysis using PBMC from the patients after ABL001 treatment**

C1D1: Pre-dosing (first cycle)
C1D2: One day after the first dosing (first cycle)
C2D1: Pre-dosing (second cycle, 28 days after the first dosing)
C2D2: One day after the second dosing (second cycle)

- Notch target genes (Hey1, Hey2, Hes1, SFRP2, SPON2), Notch pathway relators (DTX1, BCL2L1), Notch relating stemness gene (FOXO3), Vascular endothelial gene (AQP1) were analyzed




**VEGF-A concentration in plasma of the patients was decreased after ABL001 treatment**

Blue line & symbol: progression disease
Red line & symbol: stable disease
Green line & symbol: partial response

- **No correlation between PD marker change with ABL001 response so far but still PD analysis is ongoing for more solid conclusion**

## Conclusions

- ABL001 (NOV1501, TR009) therapy has been well tolerated up to 7.5 mg/kg
- No significant treatment related adverse events up to 7.5 mg/kg
- The most common treatment-related adverse events (AEs) (including all dose levels and all grades) occurred were hypertension, anemia, anorexia, general weakness, nausea, and vomiting.
- ABL001 therapy showed preliminary anti-tumor activity in heavily pre-treated cancer patients
- After completion of this ongoing phase 1a study, phase 1b/2a study is planned in combination of ABL001 with chemotherapy or anti-PD-1 antibody.

## References

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4. Lee J. et al. Journal of Cancer (in press)

## Acknowledgements

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