AACR-NCI-EORTC Virtual International Conference on
MOLECULAR TARGETS AND CANCER THERAPEUTICS
October 7-10, 2021

Phase 1a/1b Dose-escalation Study of ABL001 (CTX-009, Bispecific antibody targeting DLL4 and VEGF-A) as a Single Agent in Patients with Advanced Solid Tumors

Jeeyun Lee[1], SeungTae Kim[1], Jung Yong Hong[1], Young Suk Park[1], Joon Oh Park[1], Won Ki Kang[1], Keun-Wook Lee[2], Jin Won Kim[2], Ji-Won Kim[2], Se Hyun Kim[2], Eunsin Ha[3], Sangmi Lee[3], JongRan Kim[3], Weon-Kyoo You[3]

[1]Samsung Medical Center, Sungkyunkwan University, Seoul, South Korea; [2] Seoul National University Bundang Hospital, Seongnam-si, South Korea; [3] ABL Bio Inc., Seongnam-si, South Korea

Disclosure

Speaker Name

I have the following financial relationships to disclose:

Consultant for:

Speaker's Bureau for:

Grant/Research support from:

Stockholder in:

Employee of:

-or-I have no financial relationships to disclose.

-and-I will not discuss off label use and/or investigational use in my presentation.

-or-I will discuss the following off label use and/or investigational use in my presentation:

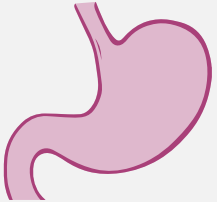
DLL4 is an Important Prognostic Factor

- DLL4 expression is a negative prognostic factor in various cancer types

Gastric cancer

48% cancer cells 22% cancer stroma

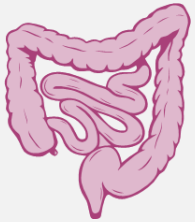
J Exp Clin Cancer Res. 2013 Jul 30;32:46.
J Cancer. 2019 Jun 2;10(14):3172-3178.



Colon cancer

71% endothelial cells

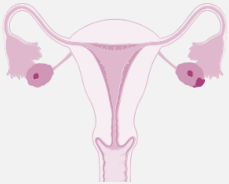
Br. J. Cancer 2009; 101:1749-1757.
Cancer Biomark. 2021 Aug 27.

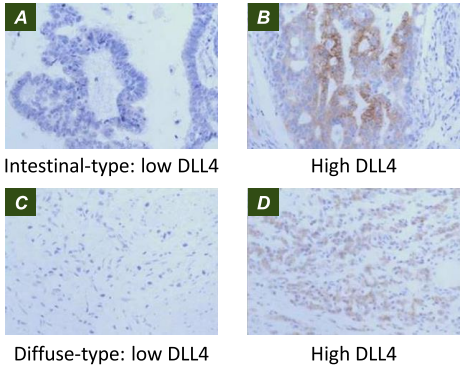


Ovarian cancer

72% cancer cells & endothelial cells

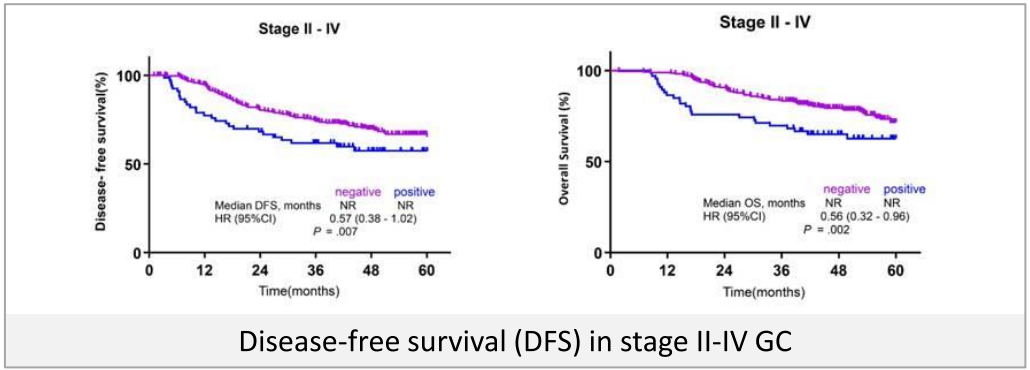
Cancer Res. 2011 Sep 15;71(18):6030-9.
Clin Chim Acta. 2014 Sep 25;436:243-8.





Intestinal-type: low DLL4 | High DLL4

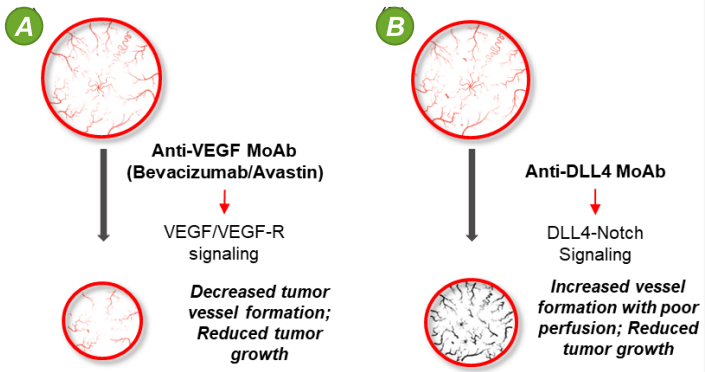
Diffuse-type: low DLL4 | High DLL4

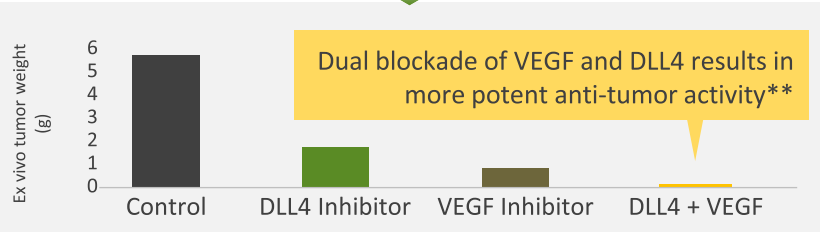


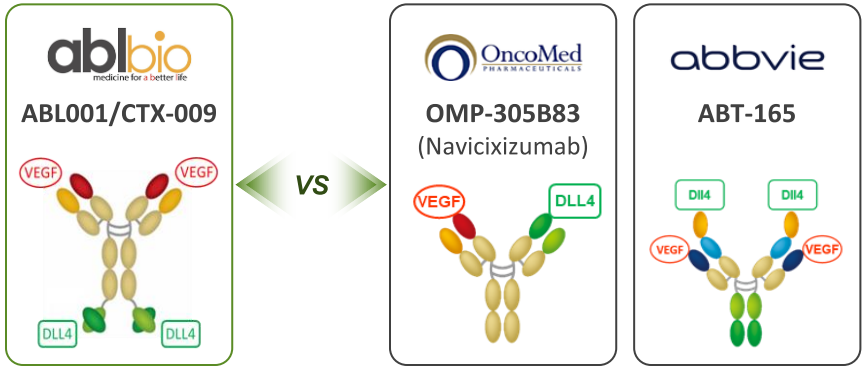
Disease-free survival (DFS) in stage II-IV GC

ABL001 (CTX-009) is a Bispecific Antibody Targeting both DLL4 and VEGF-A

Dual blockade of VEGF and DLL4 overcomes VEGF resistance*







Differentiation of ABL001 (CTX009)

- Unique proprietary DLL4 binding epitope
- Binds two each target compared to OMP-305B83
- Lower steric hindrance to bind targets compared to ABT-165

➢ Expect a better target engagement than competitors

VEGF: Vascular endothelial growth factor, DLL4: Delta-like ligand 4

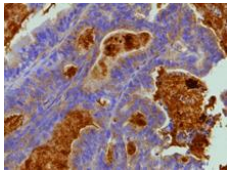
*Yin L. et al. Biochemical Pharmacology 2010, 80:690-701.
**Kuhnert F. et al. Cancer Res. 2015 Oct 1;75(19):4086-96.

Preclinical Activity of ABL001 (CTX-009)

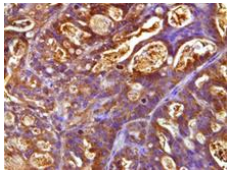
- Comparison in *in vitro* assays

Comparison	ABL001	OMP-305B83	Advantage
K_D (Human DLL4)	96 nM	10 nM	Lower toxicity due to weaker binding to DLL4
K_D (Human VEGF)	0.65 nM	8.9 nM	More potent angiogenesis inhibition by stronger VEGF blockade
VEGF/VEGFR2 competition	IC_{50} = 0.24 nM	IC_{50} = 0.64 nM	
VEGF-induced HUVEC proliferation	ED_{50} = 1.4 nM	ED_{50} = 161 nM	

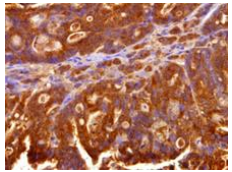
- Better *in vivo* efficacy in patient-derived xenograft (PDX) gastric cancer



DLL4++



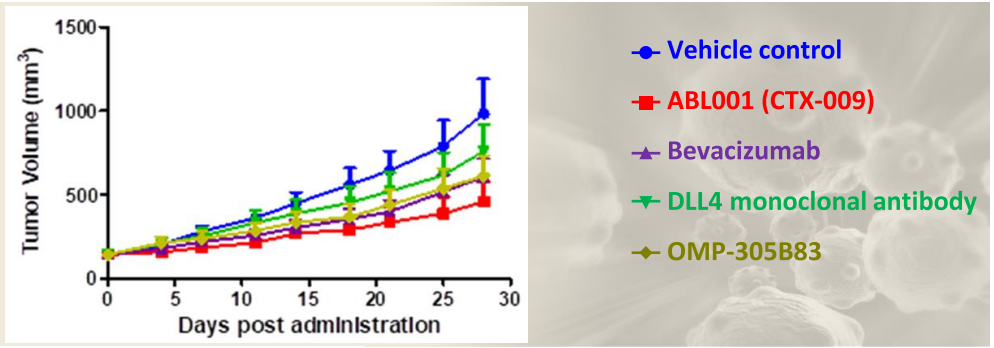
Notch1+++



*NICD+++

DLL4/Notch signaling-positive PDX

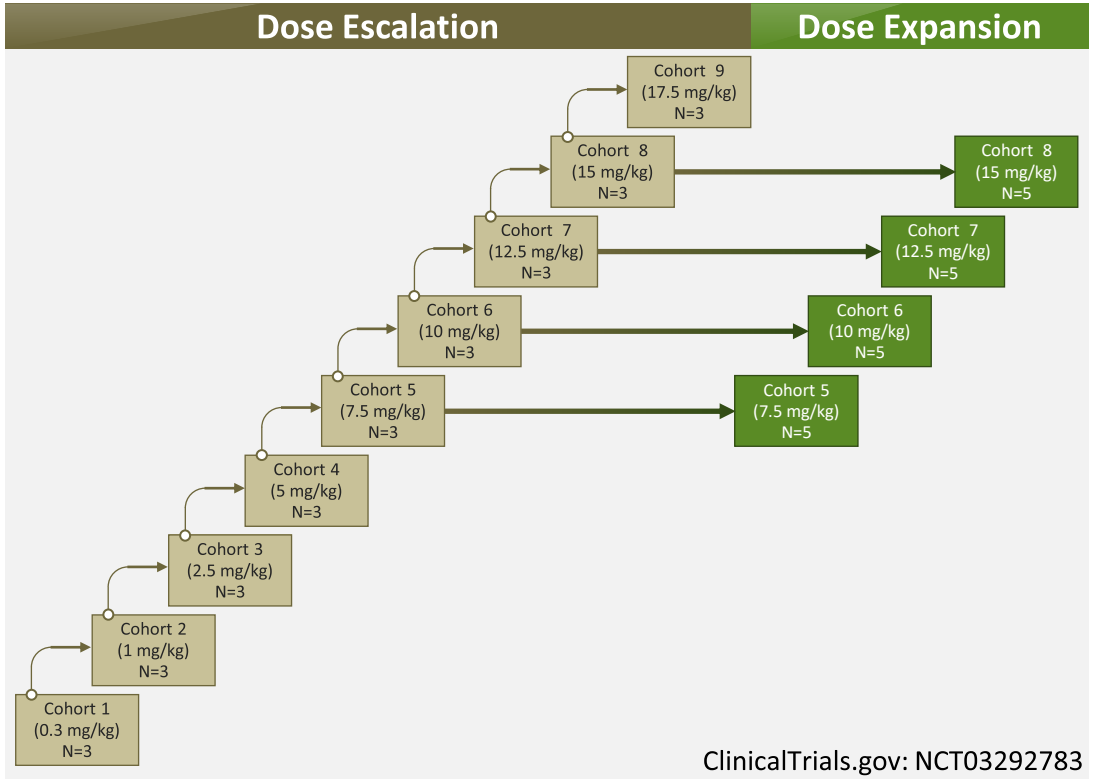
*NICD: Notch intracellular domain



Study Objective and Design

- Phase 1, multicenter, open label and first-in-human study
- Dose escalation + Dose expansion parts
- Primary objectives:

  to evaluate the safety and tolerability of ABL001 (CTX-009) and determine the MTD and RP2D
- Traditional 3+3 design for dose escalation
- Biweekly dosing



ClinicalTrials.gov: NCT03292783

Key Eligibility Criteria

Key Inclusion Criteria

- ≥19 years
- Histologically or cytologically confirmed metastatic or unresectable advanced solid tumors
- At least one measurable lesion according to the RECIST version 1.1
- ECOG Performance Status ≤ 2
- Adequate hematologic, hepatic and renal function
- Failed to standard of care

Key Exclusion Criteria

- Chemotherapy or hormone therapy within 4 weeks or 5 x half-life, anti-cancer immunotherapy within 4 weeks
- Cardiovascular diseases (ex, CHF, uncontrolled hypertension, MI, pulmonary hypertension, uncontrolled arrhythmia) within 5 years
- Bleeding disorders or digestive tract disease
- Exposure to anti-DLL4 antibodies or anti-DLL4/VEGF bispecific antibodies

CHF, Congestive Heart Failure; MI, Myocardial Infarction

Patient Demographics

	< 10 mg/kg (N=20)	≥ 10 mg/kg (N=25)	Total (N=45)
Median Age, years (range)	60 (35, 81)	51 (25, 74)	**53 (25, 81)**
Race n (%)			
Asian	20 (100.0%)	25 (100.0%)	**53 (100.0%)**
Gender n (%)			
Male	12 (60.0%)	13 (52.0%)	**25 (55.6%)**
Female	8 (40.0%)	12 (48.0%)	**20 (44.4%)**
Median Weight, kg (range)	59.7 (44.0, 85.9)	62.0 (35.6, 110.2)	**60.2 (35.6, 110.2)**
ECOG Performance Status n (%)			
0	3 (15.0%)	3 (12.0%)	**6 (13.3%)**
1	17 (85.0%)	22 (88.0%)	**39 (86.7%)**
Cancer types, n (%)			
Gastric	6 (30.0%)	13 (52.0%)	**19 (42.2%)**
Colorectal	10 (50.0%)	8 (32.0%)	**18 (40.0%)**
Other solid tumors[†]	4 (20.0%)	4 (16.0%)	**8 (17.8%)**
Prior Chemotherapy n (%)			
1	1 (5.0%)	2 (8.0%)	**3 (6.7%)**
2	1 (5.0%)	2 (8.0%)	**3 (6.7%)**
3	0	5 (20.0%)	**5 (11.1%)**
4	6 (30.0%)	8 (32.0%)	**14 (31.1%)**
≥ 5	12 (60.0%)	8 (32.0%)	**20 (44.4%)**
Prior anti-PD-1/PD-L1	6 (30.0%)	9 (36.0%)	**15 (33.3%)**
Prior VEGF inhibitor	13 (65.0%)	15 (60.0%)	**28 (62.2%)**

[†] Cholangiocarcinoma, Melanoma, Ovarian, GIST at <10 mg/kg, HCC, NSCLC, Medullary thyroid cancer, Myoepithelial carcinoma at ≥10 mg/kg

Patient Demographics

Gastric Cancer	< 10 mg/kg (N=6)	≥ 10 mg/kg (N=13)	Total (N=19)
Median Age, years (range)	60 (37, 67)	51 (33, 74)	**54 (33, 74)**
Gender n (%)			
Male	6 (100.0%)	7 (53.8%)	**13 (68.4%)**
Female	0	6 (46.2%)	**6 (31.6%)**
Median Weight, kg (range)	62.6 (51.0, 85.9)	56.1 (38.6, 88.1)	**56.1 (38.6, 88.1)**
ECOG Performance Status n (%)			
0	1 (16.7%)	1 (7.7%)	**2 (10.5%)**
1	5 (83.3%)	12 (92.3%)	**17 (89.5%)**
Prior Chemotherapy n (%)			
1	1 (16.7%)	2 (15.4%)	**3 (15.8%)**
2	0	1 (7.7%)	**1 (5.3%)**
3	0	1 (7.7%)	**1 (5.3%)**
4	2 (33.3%)	5 (38.5%)	**7 (36.8%)**
≥ 5	3 (50.0%)	4 (30.8%)	**7 (36.8%)**
Prior anti-PD-1/PD-L1	3 (50.0%)	5 (38.5%)	**8 (42.1%)**
Prior VEGF inhibitor	4 (66.7%)	7 (53.8%)	**11 (57.9%)**

Colorectal Cancer	< 10 mg/kg (N=10)	≥ 10 mg/kg (N=8)	Total (N=18)
Median Age, year (range)	62 (43, 81)	48 (25, 62)	**57 (25, 81)**
Gender n (%)			
Male	5 (50.0%)	4 (50.0%)	**9 (50.0%)**
Female	5 (50.0%)	4 (50.0%)	**9 (50.0%)**
Median Weight, kg (range)	59.65 (44.0, 74.0)	62.65 (35.6, 110.2)	**59.65 (35.6, 110.2)**
ECOG Performance Status n (%)			
0	1 (10.0%)	1 (12.5%)	**2 (11.1%)**
1	9 (90.0%)	7 (87.5%)	**16 (88.9%)**
Prior Chemotherapy n (%)			
1	0	0	**0**
2	1 (10.0%)	1 (12.5%)	**2 (11.1%)**
3	0	3 (37.5%)	**3 (16.7%)**
4	3 (30.0%)	3 (37.5%)	**6 (33.3%)**
≥ 5	6 (60.0%)	1 (12.5%)	**7 (38.9%)**
Prior anti-PD-1/PD-L1	1 (10.0%)	2 (25.0%)	**3 (16.7%)**
Prior VEGF inhibitor	9 (90.0%)	8 (100.0%)	**17 (94.4%)**

ABL001 (CTX-009) related Toxicity Profile (≥ 2 subjects, any grade)

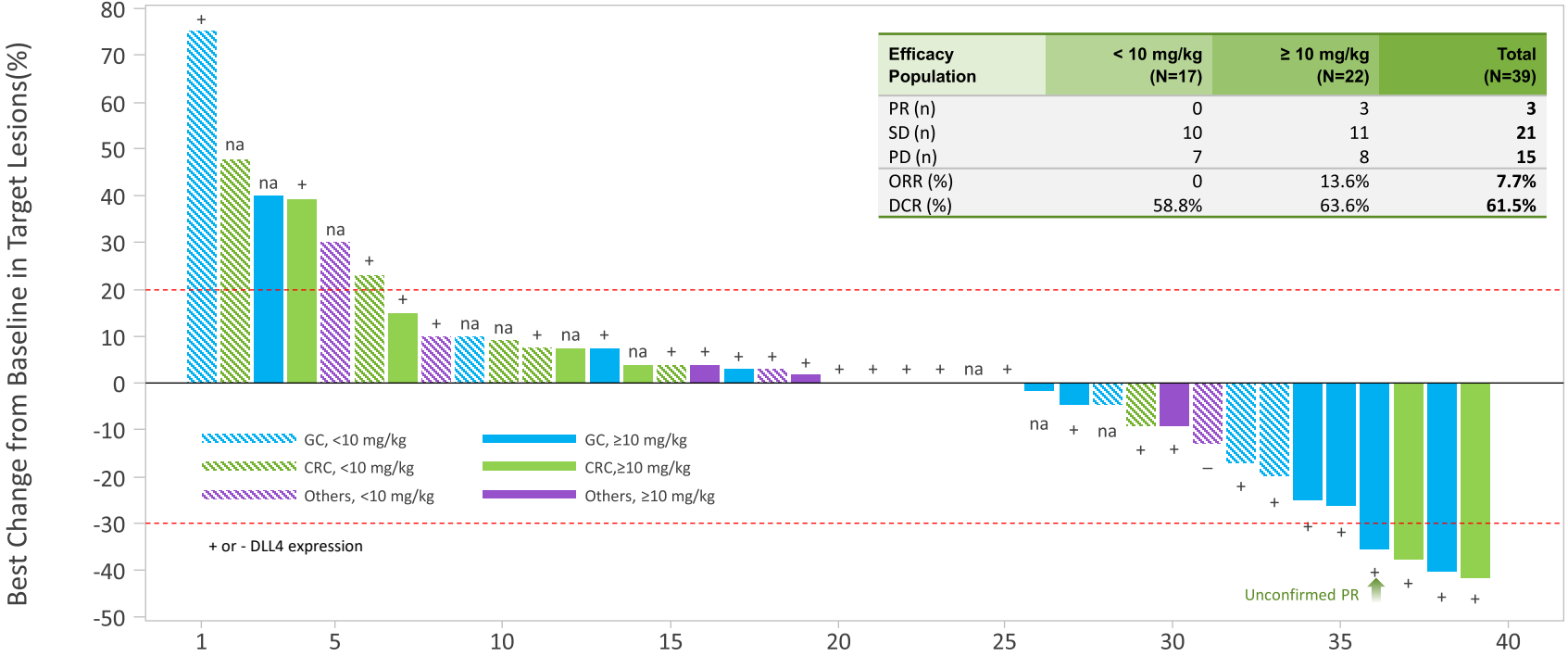
- No dose limiting toxicities (DLTs) at any dose escalation cohorts
- ABL001 (CTX-009) was well tolerated.

	Grade 1	Grade 2	Grade 3	Total (N=45)
Hypertension	1 (2.2%)	9 (20.0%)	7 (15.6%)	**17 (37.8%)**
Headache	5 (11.1%)	2 (4.4%)	0	**7 (15.6%)**
Pulmonary hypertension	3 (6.7%)	1 (2.2%)	0	**4 (8.9%)**
Proteinuria	2 (4.4%)	1 (2.2%)	0	**3 (6.7%)**
Anaemia	0	2 (4.4%)	0	**2 (4.4%)**
Fatigue	0	2 (4.4%)	0	**2 (4.4%)**
Nausea	2 (4.4%)	0	0	**2 (4.4%)**
Pyrexia	0	2 (4.4%)	0	**2 (4.4%)**

Note: Only treatment-emergent adverse events are summarized. For each preferred term, subjects are included only once, even if they experienced multiple events in that preferred term.

[†] tumor perforation, Liver carcinoma ruptured, GI perforation were reported from each one patient. Those were recovered after medical resuscitation.

ABL001 (CTX-009) Efficacy Data (N=39)

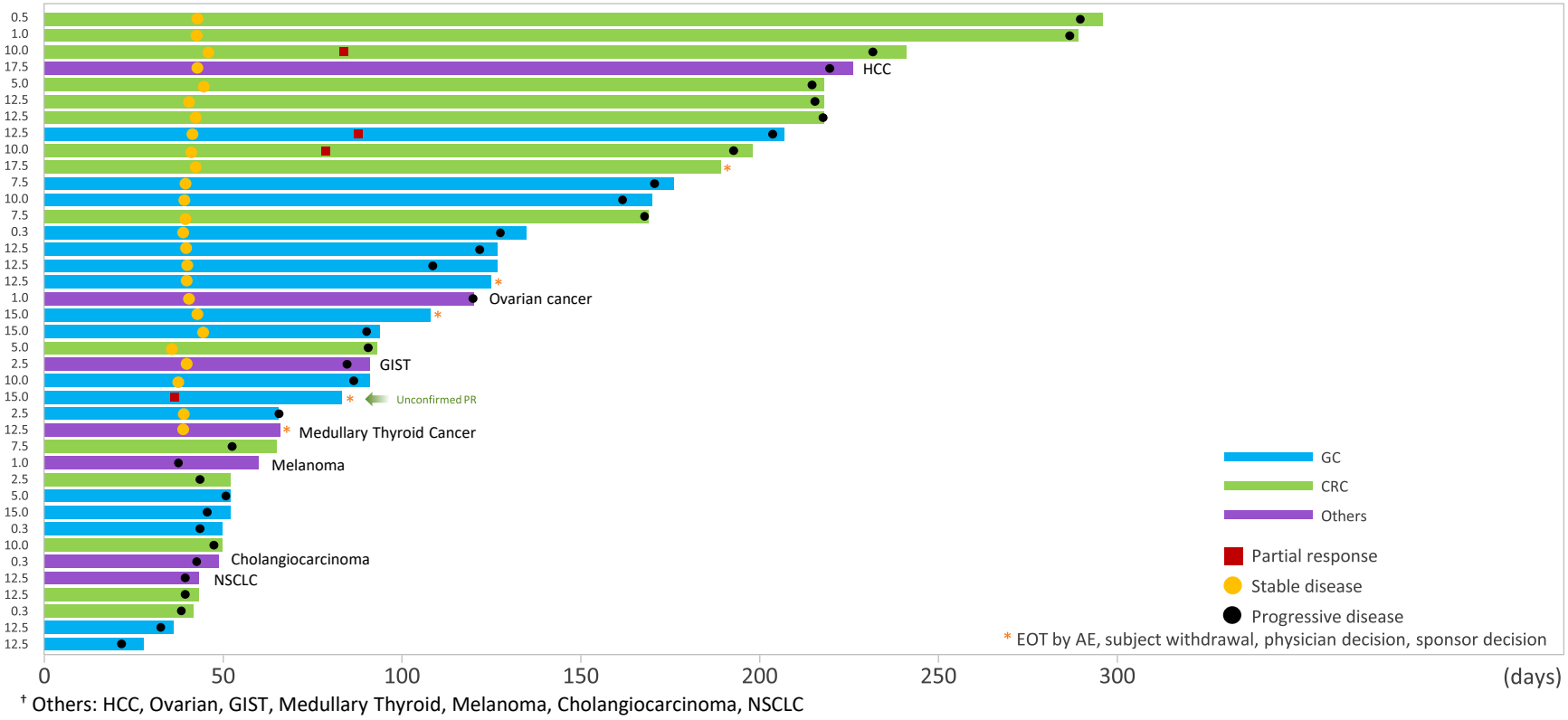


Efficacy Population	< 10 mg/kg (N=17)	≥ 10 mg/kg (N=22)	Total (N=39)
PR (n)	0	3	**3**
SD (n)	10	11	**21**
PD (n)	7	8	**15**
ORR (%)	0	13.6%	**7.7%**
DCR (%)	58.8%	63.6%	**61.5%**

PR, Partial Response; SD, Stable Disease; PD, progressive Disease; ORR, Objective Response Rate; DCR, Disease Control Rate

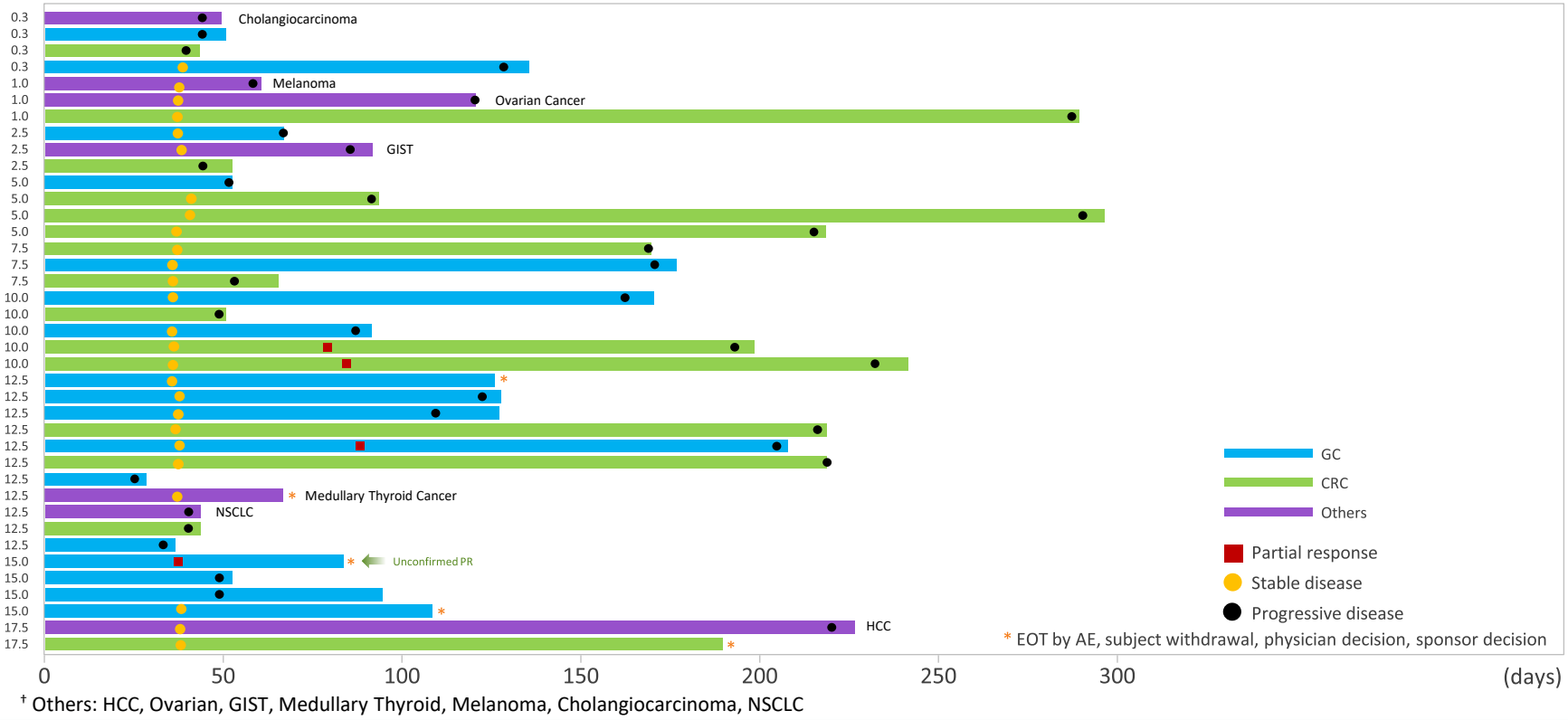
† Others: Cholangiocarcinoma, GIST, Medullar Thyroid cancer, Ovarian, HCC, NSCLC, Melanoma (in order from left to right)

Durable Responses with ABL001 (CTX-009) (N=39)



† Others: HCC, Ovarian, GIST, Medullary Thyroid, Melanoma, Cholangiocarcinoma, NSCLC

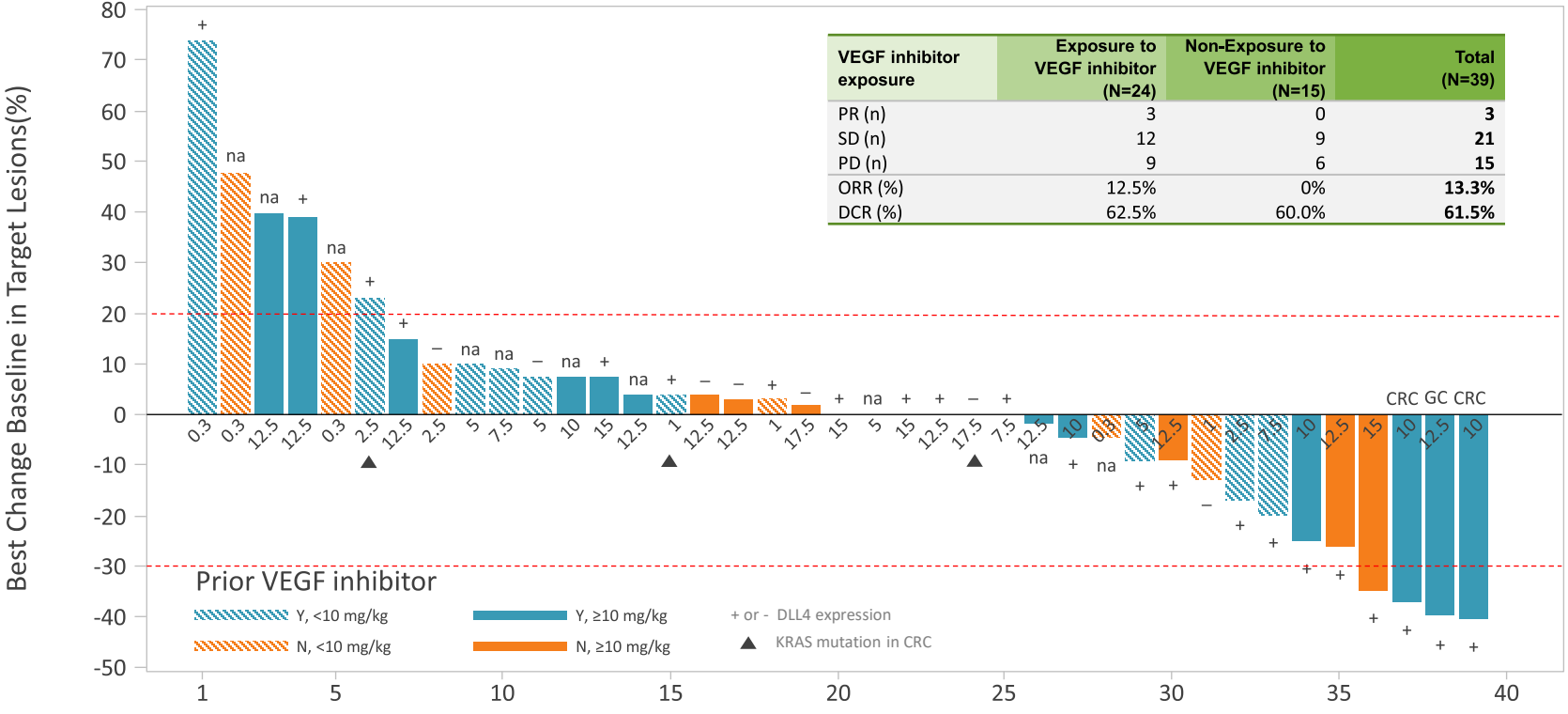
Durable Responses with ABL001 (CTX-009) (N=39)



† Others: HCC, Ovarian, GIST, Medullary Thyroid, Melanoma, Cholangiocarcinoma, NSCLC

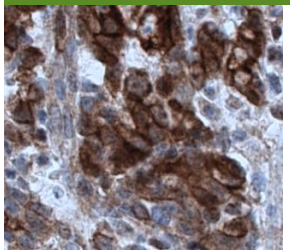
ABL001 (CTX-009) in Prior VEGF Inhibitor Exposure

VEGF inhibitor exposure	Exposure to VEGF inhibitor (N=24)	Non-Exposure to VEGF inhibitor (N=15)	Total (N=39)
PR (n)	3	0	**3**
SD (n)	12	9	**21**
PD (n)	9	6	**15**
ORR (%)	12.5%	0%	**13.3%**
DCR (%)	62.5%	60.0%	**61.5%**

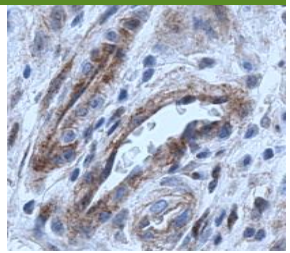


ABL001 (CTX-009) Efficacy about DLL4 Expression

GC with PR

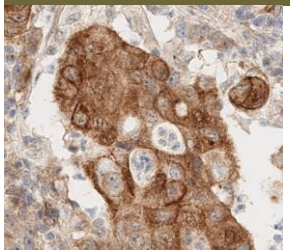


Tumor

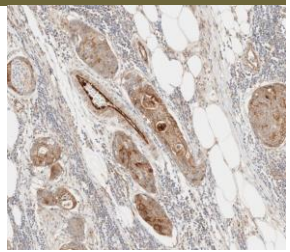


Vessel

CRC with PR



Tumor

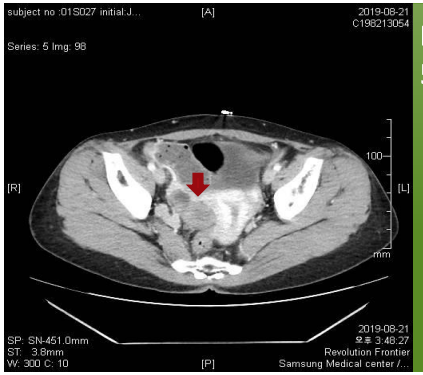


Vessel

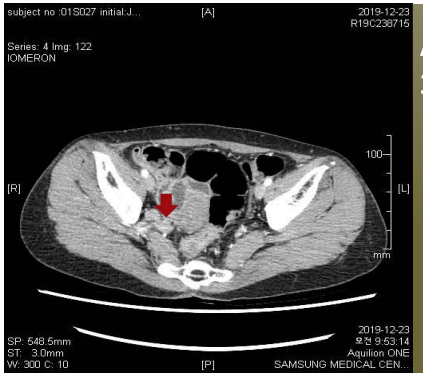
DLL4 expression	Positive	Negative	Total
ALL	N=22	N=7	**N=29**
PR (n)	3	0	**3**
SD (n)	12	5	**17**
PD (n)	7	2	**9**
ORR (%)	13.6%	0%	**10.3%**
DCR (%)	68.2%	71.4%	**69.0%**
GC	N=12	N=1	**N=13**
PR (n)	1	0	**1**
SD (n)	7	0	**7**
PD (n)	4	1	**5**
ORR (%)	8.3%	0%	**7.7%**
DCR (%)	66.7%	0%	**61.5%**
CRC	N=8	N=2	**N=10**
PR (n)	2	0	**2**
SD (n)	4	2	**6**
PD (n)	2	0	**2**
ORR (%)	25.0%	0%	**20.0%**
DCR (%)	75.0%	100.0%	**80.0%**

Confirmed Partial Response in a Gastric Cancer

- 43-yr-old Asian female patient with gastric cancer, MSS, HER2 negative
- 4 prior lines of systemic therapy
  - 1st line: CAPEOX (BR:SD)
  - 2nd line: Ramucirumab, Paclitaxel (BR:PD)
  - 3rd line: Irinotecan (BR:SD)
  - 4th line: FOLFOX (BR:SD)
- Assigned in 12.5 mg/kg dose
- Confirmed PR after 4 cycles of treatment
  - 40% decreased in the target lesion
- Duration of response: 12 weeks



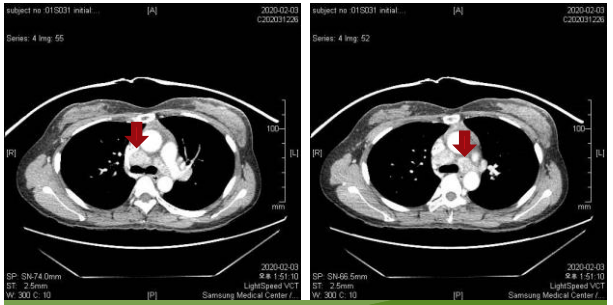
Baseline:
52 mm



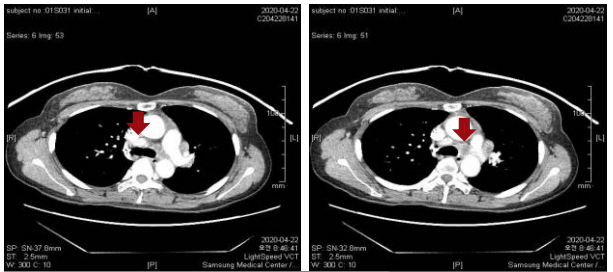
After 4 cycles:
31 mm

Confirmed Partial Response in a Colorectal Cancer

- 41-yr-old Asian female patient with colorectal cancer (KRAS wildtype)
- 4 prior lines of systemic therapy
  - 1st line: FOLFIRI, Cetuximab (PR)
  - 2nd line: Bevacizumab, Leucovorin, Oxaliplatin (SD)
  - 3rd line: Regorafenib (PR)
  - 4th line: Capecitabine (PD)
- Assigned in 10 mg/kg dose
- Confirmed PR after 4 cycles of treatment
  - 41% decreased in the target lesion
- Disease progression after 7 cycles of treatment
- Duration of response: 12 weeks



Baseline:
L1 22 mm, L2 17 mm



After 4 cycles:
L1 12 mm, L2 11 mm

In Summary

- There were no DLTs at dose escalation cohorts
- All pulmonary hypertension cases were grade 1 & 2
- In all, ORR of monotherapy is 7.7% and DCR 61.5%
- At >= 10 mg/kg, ORR was 13.6% and DCR 63.6%
- Recommend phase 2 doses (RP2Ds) were determined to be 10 mg/kg and 12.5 mg/kg

DLT, Dose Limiting Toxicity; ORR, objective Response Rate; DCR: Disease Control Rate

Conclusions

- ABL001 (CTX-009), a bispecific antibody against VEGF-A and DLL4 was well tolerated and demonstrated promising anti-tumor activity in heavily pre-treated cancer patients.
- Responders to anti-VEGF-A/DLL$ Ab were previously refractory to ramucirumab or bevacizumab.
- Combination study with chemotherapy is ongoing
- Future clinical trials can be considered in combination with anti-PD(L)1 therapy.

Acknowledgments

We would like to thank the patients, their families, and all investigators who participated in this study.

The study was funded by ABL Bio Inc. and National OncoVenture in Korea.