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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

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Disclosure

Speaker Name: Jeeyun Lee, MD

I have the following financial relationships to disclose:

Consultant for: Seattle Genetics, Mirati, AZ, Turning Point Therapeutics, Oncxerna, Medscape, Guardant Health, FivePrime

Grant/Research support from: AZ, Merck MSD, Lilly

I will not discuss 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

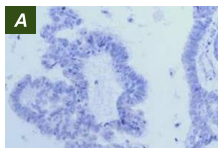
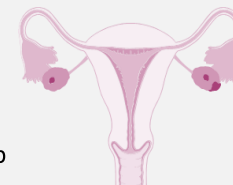
Br. J. Cancer 2009;
101:1749-1757.
Cancer Biomarker. 2021
Aug 27.



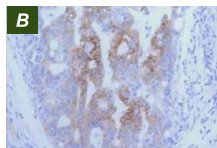
Ovarian cancer

72% cancer cells &
endothelial cells

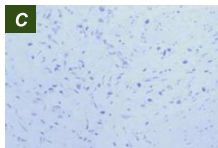
Cancer Res. 2011 Sep
15;71(18):6030-9.
Clin Chim Acta. 2014 Sep
25;436:243-8.



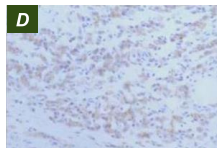
Intestinal-type: low DLL4



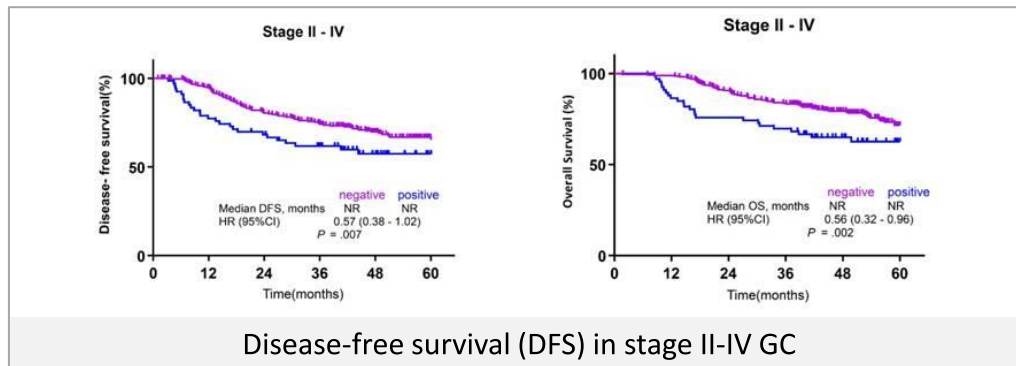
High DLL4



Diffuse-type: low DLL4

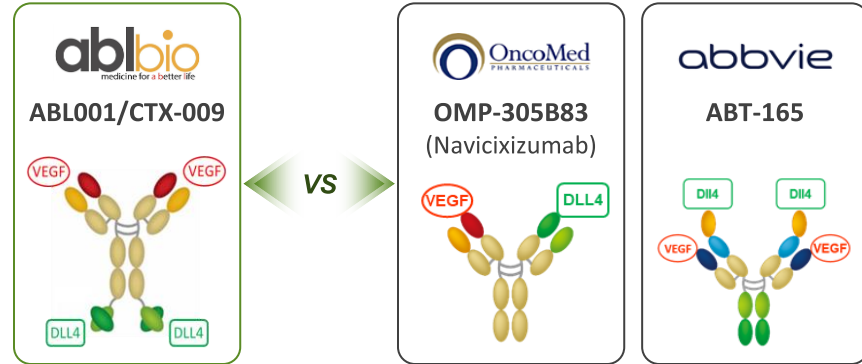
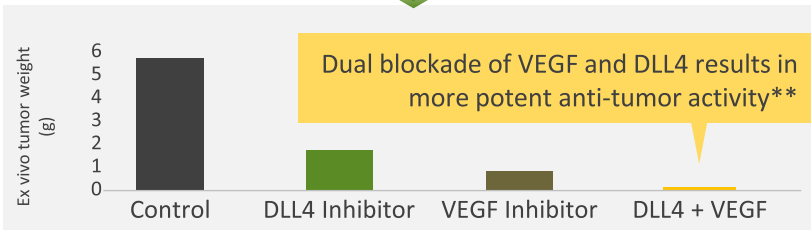
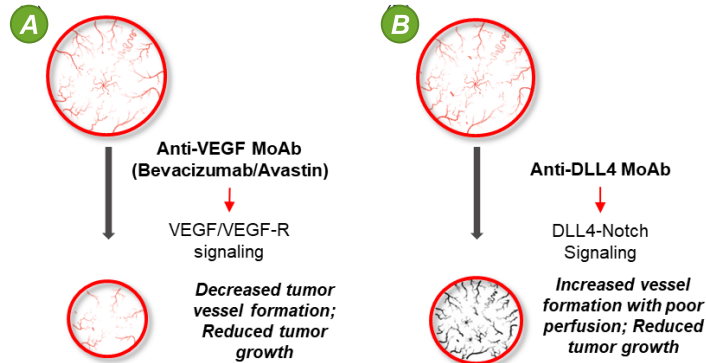


High DLL4



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.

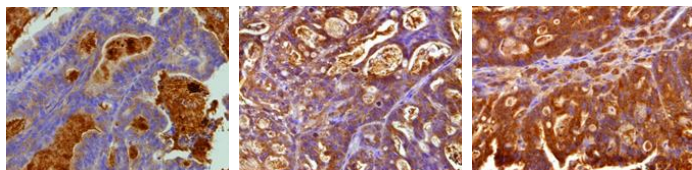
**Kuhnert F. et al. Cancer Res. 2015 Oct 1;75(19):4086-96.

Preclinical Activity of ABL001 (CTX-009)

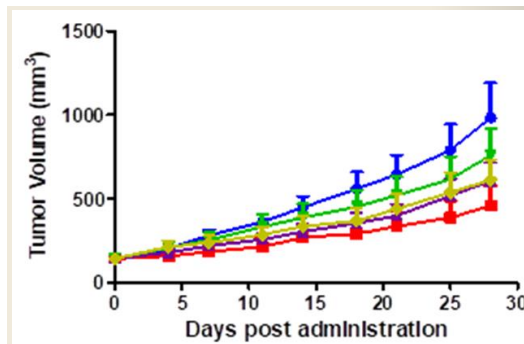
- Comparison in *in vitro* assays

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	
VEGF/VEGFR2 competition	IC ₅₀ = 0.24 nM	IC ₅₀ = 0.64 nM	More potent angiogenesis inhibition by stronger VEGF blockade
VEGF-induced HUVEC proliferation	ED ₅₀ = 1.4 nM	ED ₅₀ = 161 nM	

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



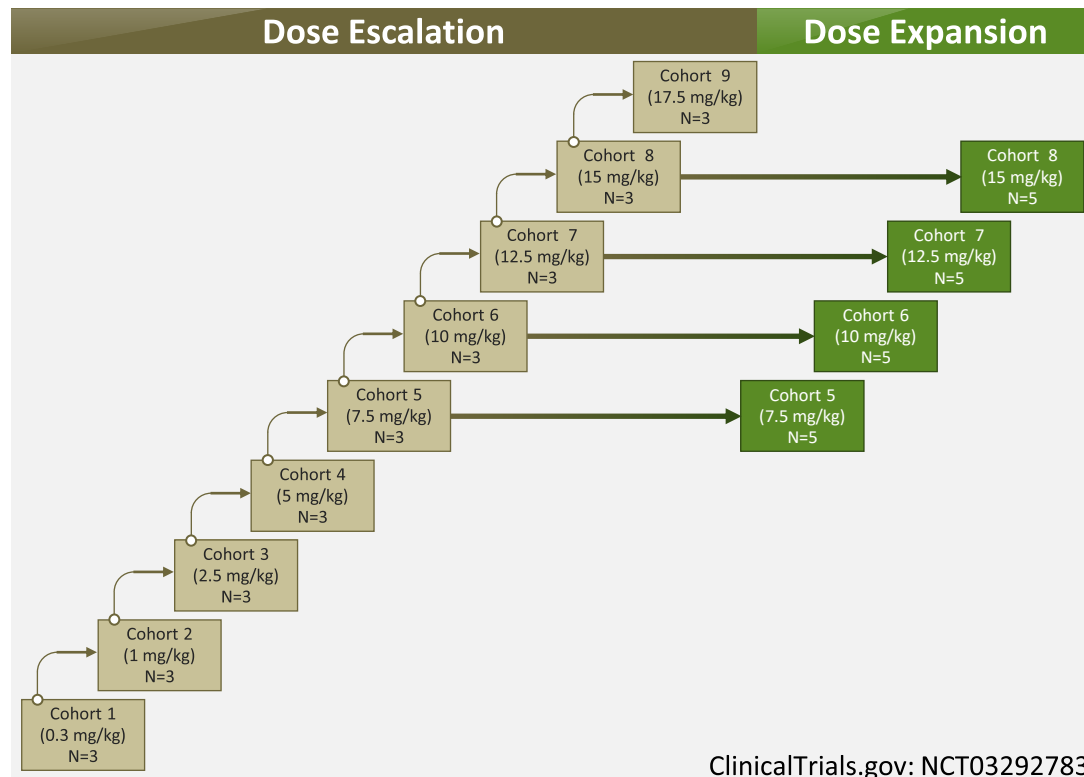
DLL4++ Notch1+++ *NICD+++
DLL4/Notch signaling-positive PDX
*NICD: Notch intracellular domain



● Vehicle control
■ ABL001 (CTX-009)
▲ Bevacizumab
▼ DLL4 monoclonal antibody
◆ OMP-305B83

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)

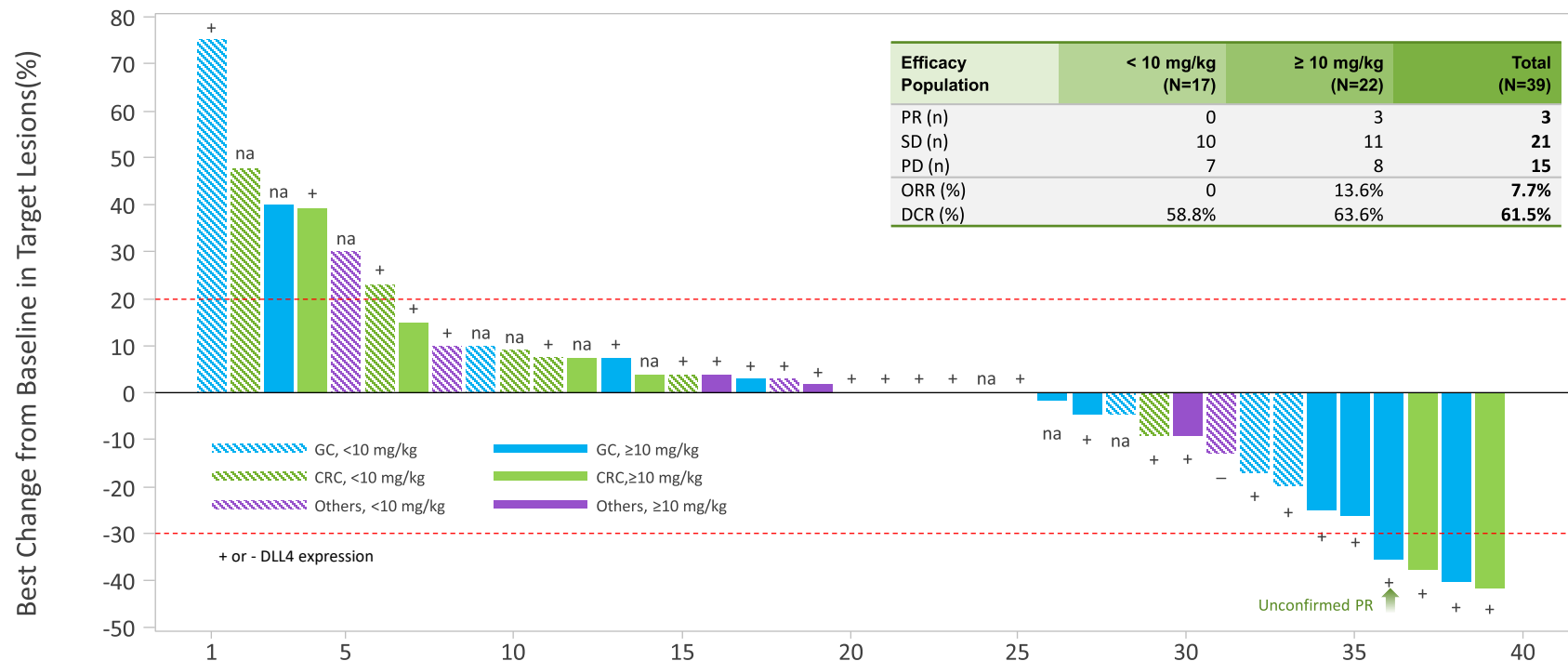
- No dose limiting toxicities (DLTs) at any dose escalation cohorts
- ABL001 (CTX-009) was well tolerated.

	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.

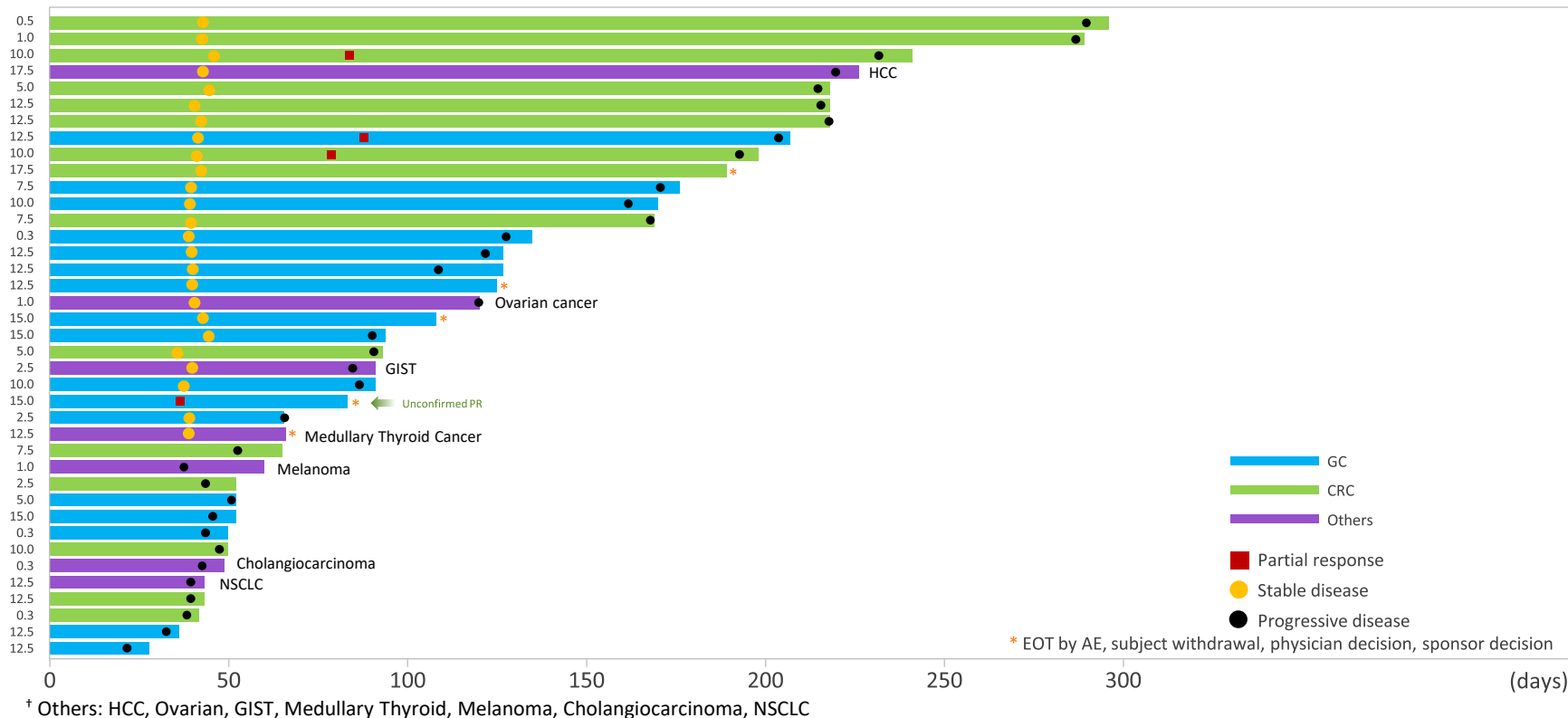
ABL001 (CTX-009) Efficacy Data (N=39)



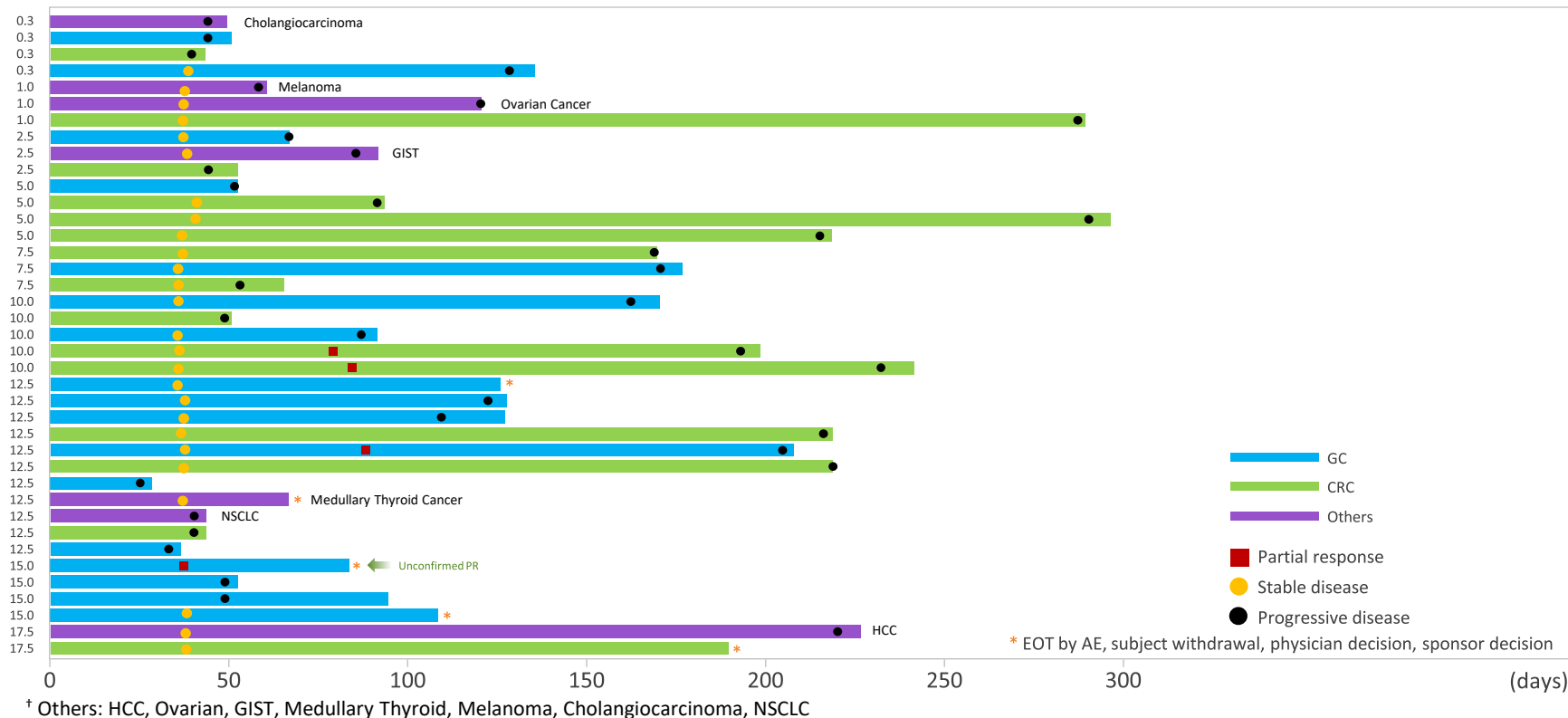
PR, Partial Response; SD, Stable Disease; PD, progressive Disease; ORR, Objective Response Rate; DCR, Disease Control Rate

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

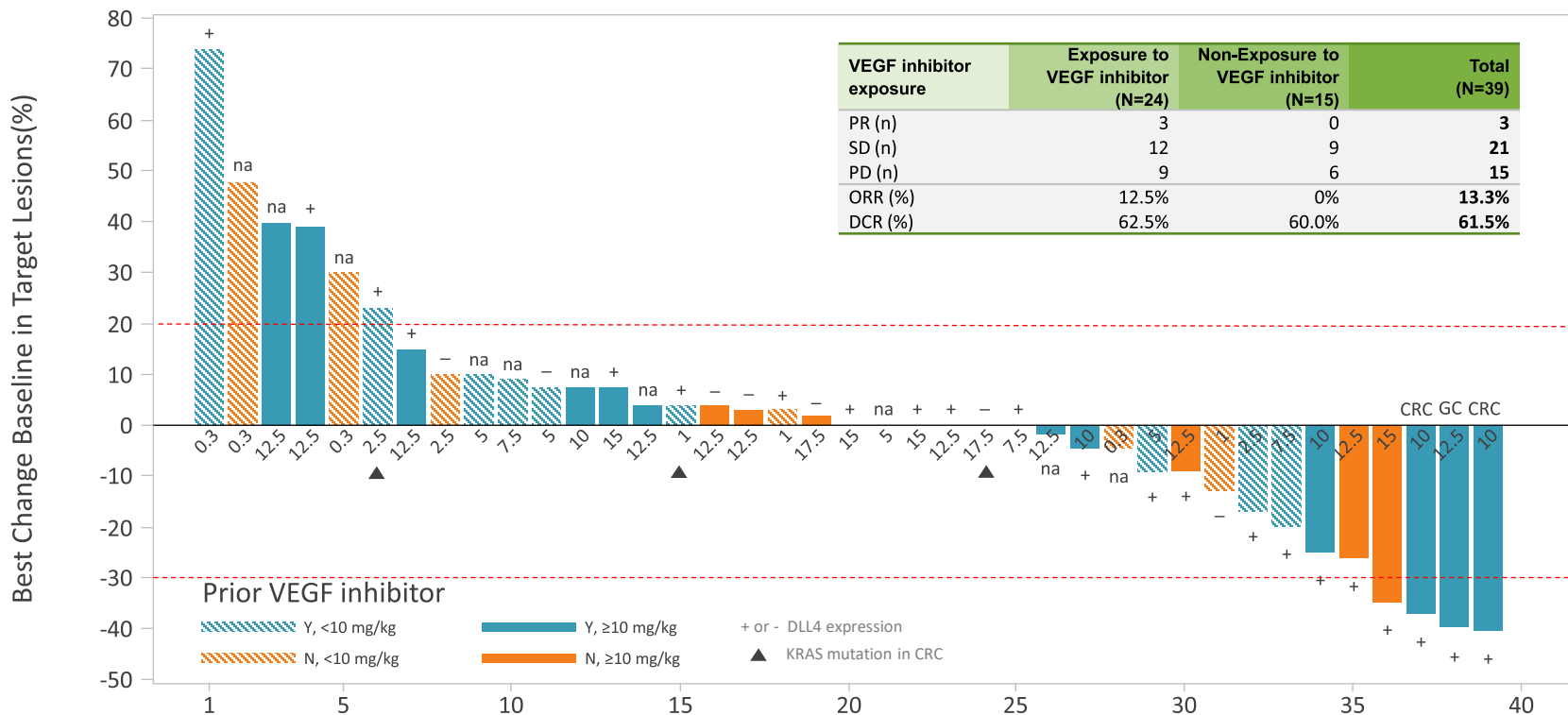
Durable Responses with ABL001 (CTX-009) (N=39)



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

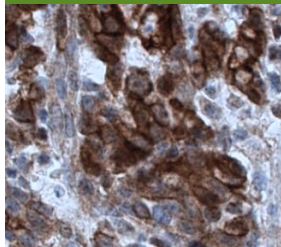


ABL001 (CTX-009) in Prior VEGF Inhibitor Exposure

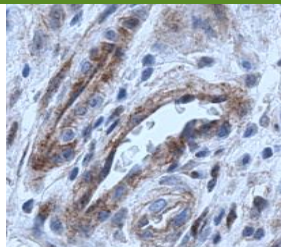


ABL001 (CTX-009) Efficacy about DLL4 Expression

GC with PR

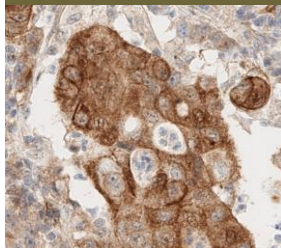


Tumor

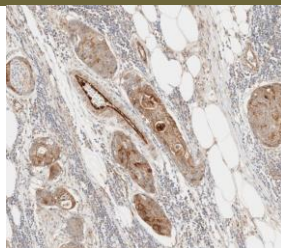


Vessel

CRC with PR



Tumor

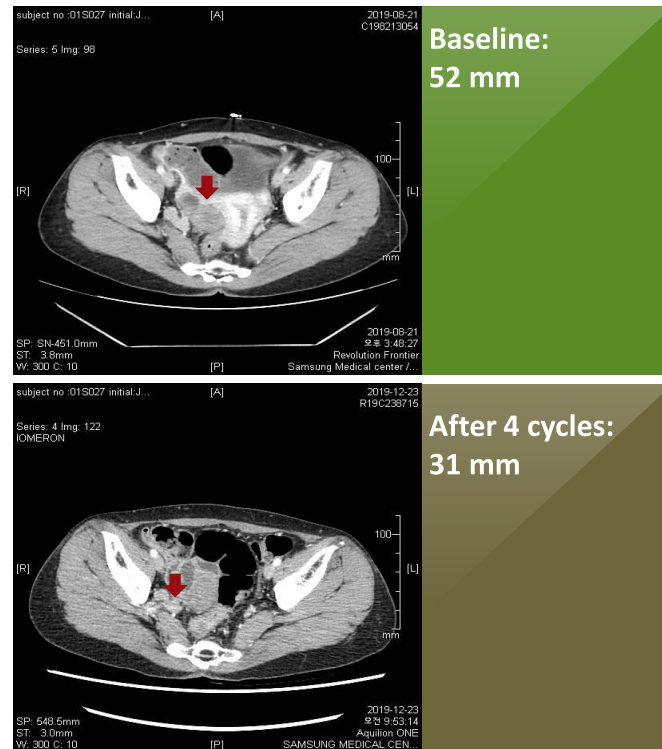


Vessel

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%

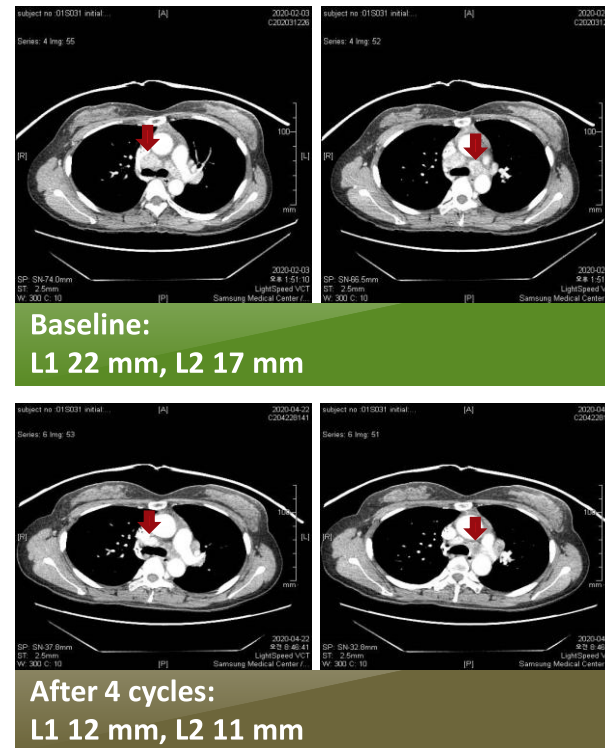
Confirmed Partial Response in a Gastric Cancer

- 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



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: FOLFOX, bevacizumab (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



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/DLL4 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.

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