First-in-human Phase 1 dose-escalation study of AV-203, a monoclonal antibody against ERBB3 in patients with metastatic or advanced solid tumors

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- · ERBB3, a unique member of the epithelial growth factor receptor (EGFR) tyrosine kinase
- Aberrantly expressed or activated in multiple human tumors^{1,2} Involved in resistance to tyrosine kinase inhibitors³
- A promising target for cancer therapeutics
- AV-203 is a superhumanized IgG1k monoclonal antibody against the ERBB3 receptor (Figure 1) with
- No binding to EGFR/ERBB1, ERBB2/HER2, ERBB4/HER4, or murine ERBB34 Potent inhibition of both ligand-dependent and independent ERBB3 signaling 4.5
- Dose-dependent inhibition of tumor growth in human cancer models⁴:
- Demonstrated ability to restore sensitivity to receptor tyrosine kinase inhibitors'

gure 1. AV-203 Mechanism of Action. NRG-1 binding of ERBB3 causes 1 receptor dimerization and activation, which is (B) blocked by AV-203.





Study Objective

 The objective of this first-in-human Phase 1 study was to evaluate the safety, tolerability, dose limiting toxicities (DLTs), maximum tolerated dose, and/or recommended Phase 2 dose (RP2D) of AV-203 in patients with advanced solid tumors (NCT01603979)

Methods

- This was a Phase 1 study of AV-203 using a 3 + 3 dose-escalation design
- · AV-203 was administered at 2, 5, 9, 14, or 20 mg/kg intravenously once every 2 weeks (1 cycle=28 days, 2 doses per cycle)
- Neuregulin 1 (NRG-1, also known as "heregulin") status was analyzed via RT-PCR analysis of formalin-fixed paraffin-embedded (FFPE) tumor tissue samples (©AltheaDx, Inc., San Diego, CA)
- · Pharmacokinetic (PK), anti-drug antibody (ADA), and pharmacodynamic (PD) bioanalyses
- were performed (PPD®, Richmond, VA) · Select eliaibility requirements include
- Patients ≥18 years of age who had histologically and/or cytologically confirmed primary diagnosis of advanced solid tumors and had progressed on standard therapie or had no proven treatment options

- Patients with hypersensitivity to recombinant proteins, significant cardiovascular disease or conduction disturbance, history of severe arrhythmia or familial arrhythmia were excluded
- Other exclusions included current or prior central nervous system or leptomeningeal metastases, thromboembolic or vascular disorders within 3 months, or positive diagnosis of hepatitis B or C or human immunodeficiency virus
- The primary objective was to determine the RP2D of AV-203; safety was evaluated through the investigation of adverse events (AEs) and DLTs
- Secondary objectives included the investigation of PK and ADA characteristics, and tumor
- Exploratory objectives included NRG-1 as a predictive biomarker and PD characteristics.

Results

- A total of 22 patients received AV-203 at doses from 2 mg/kg to 20 mg/kg (Table 1) Mean patient age was 63.9 years
- Eastern Cooperative Oncology Group performance score was 0 or 1 A total of 31.8% of patients had received ≤2 prior therapies
- Patients received a mean of 3.5 cycles of AV-203 (Table 2)
- Median time on treatment for all patients was 43 days (range: 1-603) Treatment discontinuations included 16 patients due to progressive disease
- One death occurred on study and was unrelated to AV-203 administration (progressive disease in the 2-mg/kg cohort)

	2 mg/kg (n=7)	5 mg/kg (n=3)	9 mg/kg (n=3)	14 mg/kg (n=3)	20 mg/kg (n=6)	Total (N=22)
Sex, n (%)						
Mole	4 (57.1)	2 (66.7)	3 [100.0]	2 [66.7]	4 (66.7)	15 (68.2)
Age						
Mean (SD)	62.3 (12.6)	62.3 (17.4)	64.3 [8.1]	54.3 (20.3)	71.0 (6.4)	63.9 (12.6
Race, n (%)						
White	6 (85.7)	3 [100.0]	2 (66.7)	3 (100.0)	5 (83.3)	19 (86.4)
Black	0 (0)	0 (0)	1 (33.3)	0 (0)	1 (16.7)	2 (9.1)
ECOG performance	score, n (%)					
0	5 (71.4)	1 (33.3)	1 (33.3)	1 (33.3)	0 (0)	8 (36.4)
1	2 [28.6]	2 (66.7)	2 (66.7)	2 [66.7]	6 (100.0)	14 (63.6)
Tumor type, n (%)						
Colorectal	3 [42.9]	0 (0)	1 (33.3)	0 (0)	0 (0)	4 (18.2)
sqNSCLC	0 (0)	1 (33.3)	1 (33.3)	1 (33.3)	1 (16.7)	4 (18.2)
Squamous cell, skin	0 (0)	1 (33.3)	0 (0)	1 (33.3)	0 (0)	2 (9.1)
Other solid tumors	4 (57.1)	1 (33.3)	1 (33.3)	1 (33.3)	5 (83.3)	12 (54.5)
No. of prior therap	y,5 n (%)					
±2	0 (0)	2 (66.7)	2 (66.7)	1 (33.3)	2 (33.3)	7 (31.8)
3-5	7 (100.0)	0 (0)	1 (33.3)	2 [66.7]	1 (16.7)	11 (50.0)
6-8	0 (0)	0 (0)	0 (0)	0 (0)	2 (33.3)	2 (9.1)
Unknown	0 (0)	1 (33.3)	0 (0)	0 (0)	1 (16.7)	2 (9.1)

2 mg/kg 5 mg/kg 9 mg/kg 14 mg/kg 20 mg/kg Total (n=7) (n=3) (n=3) (n=6) (N=22) No. of cycles 113.1 (216.7) 29.3 (13.5) 137.0 (115.8) 51.7 (16.8) 71.7 (31.4) 85.3 (127.6) 42 (1-603) 29 (16-43) 99 (45-267) 43 (41-71) 71 (43-102) 43 (1-603) teason for discontinuation, n (%) 1 (14.3) 2 (66.7) 0 (0) 0 (0) 1 (16.7) 4 (18.2) 4 (57.1) 1 (33.3) 3 (100.0) 3 (100.0) 5 (83.3) 16 (72.7) Patient withdrawal 1 (14.3) 0.00 0 (0) 0.101 0 (0) 1 (4.5)

- . Across all doses of AV-203, there was a single DLT that occurred in an 80-year-old patient in the 2-mg/kg cohort
- Inability to tolerate the study drug (serious grade 3 diarrhea and multiple concurrent AEs)
- The maximum administered dose of 20 mg/kg was determined to be the RP2D. The most common treatment-emergent and treatment-related AEs (all grade) were diarrhea and decreased appetite (Table 3)
- The only grade 3 or greater AEs in >1 patient were anemia, diarrhea, and hypokalemia

Table 3. All-Grade Treatment-Emergent Adverse Events in >20% of Patients and All-Grade Treatment-Related Adverse Events (N=22)

Adverse Event, n (%)	All-Grade	Treatment-Related
Diarrhea	15 (68.2)	13 (59.1)
Decreased appetite	9 (40.9)	7 (31.8)
Hypokalemia	8 (36.4)	4 (18.2)
Dry skin	8 (36.4)	7 (31.8)
Headache	7 (31.8)	0 (0)
Hypomagnesemia	7 (31.8)	6 (27.3)
Dehydration	6 (27.3)	4 (18.2)
Dizziness	6 (27.3)	2 (9.1)
Dyspnea	6 (27.3)	0 (0)
Nausea	6 (27.3)	3 (13.6)
Anxiety	5 (22.7)	1 (4.5)
Depression	5 (22.7)	0 (0)
Foligue	5 (22.7)	4 (18.2)

PK, ADA, and PD Characteristics

- PK analysis indicates AV-203 levels are approximately dose proportional [Table 4]
- · No detection of ADAs were observed
- At all AV-203 dose levels, ERBB3 levels rose by approximately 5-fold from baseline by cycle 1 day 15 and sustained these levels through cycle 2 day 15 (Figure 2)

- . One partial response that lasted 6 cycles was confirmed in Patient 1 (Figure 3) in the 9-mg/kg cohort with squamous non-small cell lung cancer (sqNSCLC)
- · Stable disease was the best response for 8 patients
- Patient 2 (Figure 3) demonstrated long-term stable disease lasting at least 22 cycles

igure 3. Patient Response Summaries.

Patient 1 - sqNSCLC with partial response (9 mg/kg)

- Diagnosed December 5, 2007
- Prior therapies Cisplatin/etoposide [[neoladiuvant,
- May-July 2008|
 Carboplatin/taxane (June-November 2011)
 Gemcitabine (March-October 2012)
- Started AV-203 November 2012 Partial response detected at the end of cycle 4 and lasted for 6 cycles
- Reduction of 34% in sum of the longest diameter of target lesion (17% at cycle 2)
- NRG-1 status from baseline tumor
- specimen: Positive



Patient 2 - metastatic endometrial biphasic stromal cancer with long-term stable disease (2 mg/kg)

- Diagnosed March 16, 2009.
- Prior therapies
- Combination chematherapy, including carboplatin and pacifiaxel Following progressive disease, treated with investigational anti-endoglin antibody
- Started AV-203 July 2013
- Jantea Av-203 July 2013
 Received >22 cycles with continued stable disease and no DTs or dose reductions
 Non-partial response reduction in target lesion and stable to slightly improved non-larget lesions per RECIST

 NRG-1 status from baseline tumor specimen: Negative



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5 mg/kg 9 mg/kg (n=3) 215.3 (15.6)

· Of 20 subjects providing predose samples, 14 were analyzed for NRG-1 by RT-PCR and

12 could be correlated to an evaluable response (Table 5)

Patient	NRG-1 Status	Tumor Type	Overall Response
1	Positive	sgNSCLC	PR
2	Negative	Stroma tumorendometria	Long-term SD
3	Negative	Peritoned	PD
4	Positive	Squamous cell carcinoma of the skin	PD
5	Negative	sgNSCLC	PD
6	Negative	Rectal adenocarcinoma	SD
7	Indeterminate	Hepatool dar carcinoma	PD
8	Indeterminate	sgNSCIC	PD
9	Negative	SCCHN	PD
10	Negative	Neurendocrine tumor of the stomach	SD
11	Negative	Blodder	SD
12	Negative	Cervico	SD

Conclusions

- · Maximum planned dose of AV-203 monotherapy was reached with 1 DLT - RP2D is 20 mg/kg intravenously every 2 weeks
- Most common AEs were diarrhea and decreased appetite PK results indicated dose-proportional levels of AV-203
- No detection of ADAs was observed
- · PD analysis showed ERBB3 levels were increased approximately 5-fold
- Expression of NRG-1 in the sqNSCLC patient with the partial response may indicate the potential to use NRG-1 as a predictive biomarker for patient selection

 The partial response in a patient with sqNSCLC, as well as the long-term stable disease
- ved, indicates that AV-203 warrants further investigation as an anticancer therapy

NRG-1 Analysis

- References

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