A Phase I, first-in-human study of ARGX-111, a monoclonal antibody targeting c-Met in patients with solid tumors

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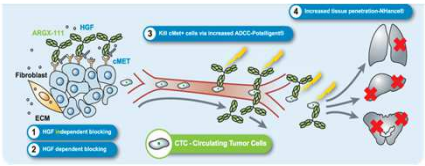
ABSTRACT

Dysregulation of the tyrosine kinase receptor c-Met, is associated with tumorigenesis, metastasis and progression via hepatocyte growth factor (HGF)-dependent or-independent mechanisms. ARGX-111, a monoclonal IgG1 SIMPLE Antibody™ glyco-engineered for enhanced ADCC properties (POTELLIGENT®), is currently investigated in a Phase 1 clinical trial (accelerated titration design) in patients with advanced solid tumors (NCT 02055066). As of March 2015, 18 patients (median age: 56 years; prior chemotherapy/targeted therapies/biological therapies: 89%/28%/33%;) with tumors staining positive (> 50% of tumor cells) for c-Met by immunohistochemistry have been treated at 4 dose levels (0.3, 1, 3, and 10 mg/kg IV q3 weeks; n = 2, 2, 11, and 3, respectively) and received a total of 57 cycles (median = 2; range 1-9). Patients with different histologies were enrolled (4 upper GI, 3 RCC, 3 pancreas, 2 NSCLC, 2 cervix, 1 breast and 3 others). The most common drug-related adverse events (AE) were: infusion-related reaction (IRR) (70%), fatigue (29%) and nausea (24%). Drug-related Grade 3 AEs (IRRs) were observed in 2 patients. The MTD was 3 mg/kg IV q3 weeks. C_{max} and AUC were dose-linear, with a half-life of 3-4 days. Serum HGF levels remained stable during treatment. Ex vivo ADCC was observed in all patients and NK cell counts remained stable during treatment across all dose levels.

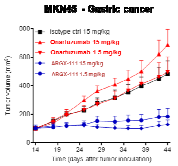
One patient with metastatic, c-Met amplified gastric cancer refractory to platinum and taxane-based chemotherapy regimens, was treated at 0.3 mg/kg (escalated to 1.0 mg/kg) and maintained stable disease by RECIST for 6 months, associated with mixed metabolic response on PET scan, and a more than 50% reduction in CTCs. Recruitment of the safety expansion cohort (c-Met amplified) is ongoing.

BACKGROUND

Different modes of action of ARGX-111

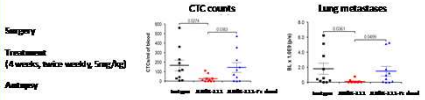


Blocking of c-Met amplified tumor growth



- Potent inhibition of c-Met amplified tumor cell line MKN-45 in mouse xenograft model

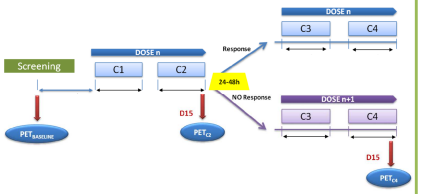
Suppression of metastasis by CTC reduction



- Depletion of CTCs by c-Met-targeted ADCC is an effective strategy to prevent tumor recurrence and suppress metastatic dissemination

MATERIALS AND METHODS

Accelerated titration design based on PET/CT



Study objectives

Primary:

- To determine the MTD and recommended Phase 2 dose (RP2D) of ARGX-111

Secondary:

- Characterize safety profile of ARGX 111
- Characterize pharmacokinetics (PK) and immunogenicity of ARGX 111
- Characterize biomarkers of ARGX-111 activity (PD)
- Document preliminary evidence of antitumor efficacy

Main inclusion criteria

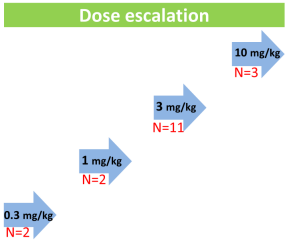
- Age ≥18 years
- Written informed consent
- Histological/cytological diagnosis of cancer
- Cancer relapsing after or refractory to standard therapy
- Over-expression of c-Met (> 50% of cells; 2+/3+ intensity)
- ECOG performance status of 0 or 1
- Adequate haematological hepatic and renal function
- At least one tumor lesion > 2 cm on 18F-FDG PET/CT

RESULTS

Patient characteristics

	N=18
Gender M:F	**11:7**
Median age (range)	**56 (28-71)**
Prior therapy	**Chemo: 89% Targeted (TKI): 28% Biological (mAbs): 33%**
Histologies	**4 Gastric/esophagus 3 RCC 3 pancreas 2 NSCLC 2 cervix 1 breast 3 others**

Drug exposure



- Innovative accelerated titration design based on PET/CT with intrapatient dose escalation allowed for rapid dose escalation (time to MTD determination was 8 months)
- Premedication with acetaminophen, H1 & H2 blockers and steroids administered prior to each cycle
- Most patients treated at 3 mg/kg cohort (N=11) and most cycles given at 3 mg/kg (n=27)

Safety profile

AE grouping	Number patients with AE N	Number patients with drug-related AE N
All grades	**17**	**14**
Grade 3-4	**9**	**3**
Dose limiting (Cycle 1)	**2**	**2**

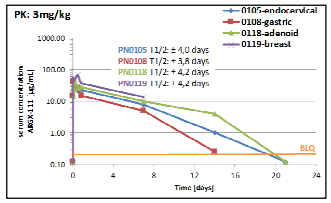
- Two dose-limiting events were observed in the 10 mg/kg cohort
- MTD is established at 3 mg/kg IV q3 weeks
- Most common drug-related adverse events are Infusion Related Reactions (IRR) (70%), fatigue (29%), nausea (24%), back pain (18%), arthralgia (18%) and myalgia (18%)
- Most common drug related grade 3 are IRR, back pain and pain in extremities

Biomarker results

Dose level	0.3 mg/kg (n=2)	1 mg/kg (n=2)	3 mg/kg (n=4)	10 mg/kg (n=3)
C_{max}(mean) (µg/ml)	5.6	11.4	43.4	113.2
ADA	No	No	No	No
HGF levels	Stable	Stable	Stable	ND
ADCC	Yes	Yes	Yes	Yes
NK-cell count	Stable	Stable	Stable	Stable

- C_{max} and AUC were dose-linear, with a median half-life of 3-4 days
- All other biomarkers show no dose-effect

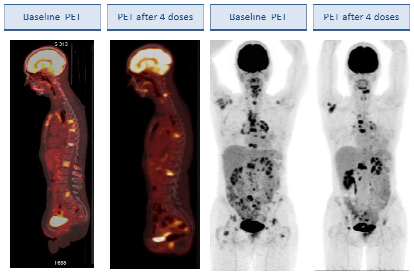
PK profile



- Dose selection for safety expansion based on PK profile at 3 mg/kg: q2w dosing maintains C_{trough} above 3 µg/ml

Activity in gastric patient with bone and lymph node metastasis

- 50 year old; metastatic gastric cancer with metastasis to bone and lymph nodes
- Only patient with c-Met amplification on study (1/16)
- 2 prior lines of triplet chemotherapy
- Patient treated with 0,3 mg/kg ARGX-111 (escalated to 1 mg/kg after 2 cycles)
- CTCs reduced by 75%
- ECOG performance status maintained



CONCLUSIONS

- Innovative trial design allowed for rapid dose escalation
- MTD determined at 3 mg/kg
- Early signs of activity observed in patient with gastric c-Met amplified cancer by PET/CT scan and CTC reduction. This confirms the clinical mechanism of action of ARGX-111

FUTURE DIRECTIONS

- The combined safety and efficacy data of this phase 1b dose escalation study strongly supports the further development in c-Met amplified malignancies. The safety expansion portion of this phase 1b study will focus on this type of patients
- Based on PK data the dosing schedule will be 3 mg/kg every 2 weeks