

Phase 1 study of the toll-like receptor 9 (TLR9) agonist, IMO-2055, combined with erlotinib and bevacizumab in patients with advanced or metastatic non-small cell lung cancer

David Smith,¹ Paul Conkling,² Don Richards,³ Carlos Alemany,⁴ Thomas Boyd,⁵ Lawrence Garbo,⁶ David Loesch,⁷ David Wages,⁸ Alice Bexon,⁹ Jessica Murphy⁹
¹US Oncology, Vancouver, WA; ²US Oncology, Norfolk, VA; ³US Oncology, Tyler, TX; ⁴US Oncology, Ocoee, FL; ⁵US Oncology, Yakima, WA; ⁶US Oncology, Albany, NY; ⁷US Oncology, Indianapolis, IN; ⁸EMD Serono, Rockland, MA; ⁹Idera Pharmaceuticals, Cambridge, MA, USA

BACKGROUND/RATIONALE

- IMO-2055 is a novel synthetic oligonucleotide agonist of Toll-like receptor 9 (TLR9) under development for the treatment of solid tumors.
- IMO-2055 induces a Th1-type innate immune response that, in turn, stimulates further innate and adaptive immune responses in preclinical studies.¹⁻³
- IMO-2055 or its murine analog showed single-agent anti-tumor activity against human colon, lung, breast, prostate, non-Hodgkin's lymphoma, and melanoma tumors in preclinical models.³
- In combination with cytotoxics, targeted therapies or monoclonal antibodies, IMO-2055 or its murine analog showed additive or synergistic anti-tumor activity across various solid tumor models:
 - erlotinib and bevacizumab in lung models⁴
 - bevacizumab in colorectal models^{5,6}
 - cetuximab in colorectal models^{5,6}
 - gemcitabine in an NSCLC model.⁷
- A phase 1 study in healthy subjects demonstrated the safety of IMO-2055 dosages from 0.005 to 0.16 mg/kg/wk SC and IV and showed dose-dependent immune system activation.⁴
- IMO-2055 was well tolerated in a phase 1 single-agent study in refractory solid tumor patients at dosages from 0.04 to 0.64 mg/kg/week SC, demonstrating immune system activation and evidence of long-lasting stable disease.⁸ Adverse events (AEs) were mild-to-moderate injection site reactions and flu-like symptoms.
- IMO-2055 has shown promising efficacy in combination with gemcitabine and carboplatin in patients with pretreated advanced NSCLC in a phase 1 study.⁹
- Erlotinib¹⁰ and bevacizumab¹¹ are FDA-approved agents for the treatment of advanced NSCLC. In addition, two studies that were ongoing at the time of protocol development (Genentech's phase 3 ATLAS trial¹² and phase 3 BeTa¹³ Lung trial) have now reported improvements of PFS when erlotinib and bevacizumab are used in combination. In the BeTa trial, the median PFS was 15 weeks with erlotinib and bevacizumab combination.
- Based on these data, we investigated the safety and tolerability of the combination of IMO-2055 with erlotinib and bevacizumab in a phase 1b study in patients with advanced/metastatic NSCLC.

STUDY DESIGN

- Patient selection and study design are summarized in Figure 1.
- Patients were included with histologically proven AJCC stage III/IV advanced/metastatic NSCLC not amenable to curative therapy, progression during or after first-line therapy, and ECOG score 0/1. Patients with intrathoracic squamous disease were excluded.
- Dose-finding, open-label phase 1b study at US centers (n=9), with a dose escalation phase followed by expansion at a potential phase 2 dose.
- Treatment involved 3-weekly cycles of fixed-dose bevacizumab / erlotinib with escalating doses of IMO-2055 using a classic 3+3 design.
 - bevacizumab IV: 15 mg/kg on d1
 - erlotinib PO: 150 mg daily
 - IMO-2055 SC on d1, 8, and 15:
 - 0.08 mg/kg/wk
 - 0.16 mg/kg/wk
 - 0.32 mg/kg/wk
 - 0.48 mg/kg/wk.
- Treatment continued until disease progression or another protocol-specified stopping criterion was met.
- AEs were graded according to NCI-CTCAE (v3.0). DLT was defined as:
 - grade 4 hematological AE for >5 days
 - grade ≥3 nausea, diarrhea, or vomiting despite maximal supportive care and/or prophylaxis
 - any grade ≥3 clinically significant non-hematological AE
 - treatment delay >14 days due to recovery from drug-related grade ≥2 AE
 - AE leading to erlotinib interruption >5 days.
- Response classification was based on RECIST.

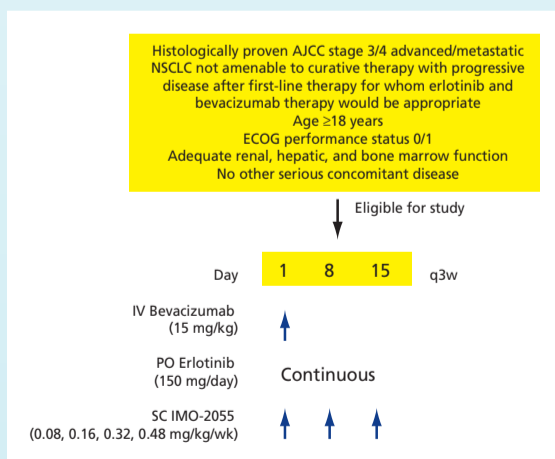


Figure 1. Study design and treatment schedule

BASELINE CHARACTERISTICS

- 20 patients were enrolled and treated between December 2007 and May 2009.
- 16 patients were enrolled in the dose escalation portion of the study
- Up to May 2009, four additional patients have been enrolled to the expanded 0.32 mg/kg/wk dose level.
- Baseline patient characteristics are shown in Table 1.

Table 1. Baseline patient characteristics (n=20)

	No. of patients	(%)
Male/female	11/9	55/45
Median age, years (range)	66 (53-83)	
Race		
White	17	85
Black	3	15
ECOG performance status		
0	5	25
1	13	65
Unknown	2	10
Histopathology		
Adenocarcinoma	15	75
Squamous cell carcinoma	2	10
Large cell carcinoma	2	10
Unknown	1	5
No. of prior chemotherapy regimens*		
0	1	5
1	12	60
≥2	5	25
Unknown	2	10
Prior radiotherapy		
Yes	7	35
No	11	55
Unknown	2	10
Number of metastatic sites		
0	5	25
1	7	35
≥2	6	30
Unknown	2	10
Metastatic site(s)		
Liver	4	20
Lung	3	15
Lymph nodes	7	35
Other	6	30

*15 (83%) and 17 (94%) patients had received at least one prior taxane-containing and platinum-containing regimen, respectively.

EXPOSURE TO STUDY DRUGS

- Sixteen patients were enrolled in the dose-escalation portion of the study. All 16 patients eventually discontinued treatment due to: disease progression (n=4), adverse events (n=8), patient decision (n=3), and death unrelated to treatment (n=1).
 - Eight of the 16 patients had received 18 weeks of treatment, 4 had received 27 weeks of treatment, 3 had received 30 weeks of treatment and 2 had received at least 52 weeks of treatment.
- As of August 27, 2009, 3 patients enrolled to the expanded 0.32 mg/kg/wk arm discontinued treatment due to disease progression and 1 patient continued on trial.

SAFETY OF IMO-2055 + ERLOTINIB/BEVACIZUMAB THERAPY

- 20 patients were evaluable for safety.
- DLTs were grade 3 anorexia, dehydration, and acneiform rash (face) in 1 patient at 0.16 mg/kg/wk and grade 3 fatigue in 1 patient at 0.48 mg/kg/wk.
- The maximum tolerated dose was not reached at the highest IMO-2055 dose level evaluated in the dose escalation phase (0.48 mg/kg/wk).
- Further dose escalation was not considered based on previous pharmacodynamic data from prior studies^{4,5} and the observation of 1 DLT at 0.48 mg/kg/wk.
- There have been no treatment-related deaths.
- Most common treatment-related AEs (any grade) have been injection site reaction (63%), diarrhea (50%), fatigue (44%), nausea (32%), and anorexia (25%), with 1 treatment-related serious AE (the above-cited DLT of grade 3 anorexia, dehydration, and rash)
- Treatment-related hematological AEs are shown in Table 2.
- There was only 1 grade 3 hematological AE (anemia), which was possibly related to treatment and occurred at the lowest dose cohort (0.08 mg/kg/wk).
- Treatment-related non-hematological AEs during IMO-2055 + erlotinib/bevacizumab therapy are shown in Table 3.
- Grade 3 non-hematological AEs were: diarrhea, fatigue, hypokalemia, and injection site reaction. There were no grade 4 non-hematological AEs

Table 2. All treatment-related (possible, probable, definite) hematological AEs: number of patients (%)*

AEs, n (%)	Cohort (IMO-2055 dose)				Total (N=20)
	0.08 mg/kg (n=4)	0.16 mg/kg (n=6)	0.32 mg/kg (n=7)	0.48 mg/kg (n=3)	
Anemia					
Grade 1/2	0 (0)	2 (33)	2 (29)	1 (33)	5 (25)
Grade 3	1 (25)	0 (0)	0 (0)	0 (0)	1 (5)
Neutropenia					
Grade 1	0 (0)	1 (17)	0 (0)	0 (0)	1 (5)
Thrombocytopenia					
Grade 1	0	0	1 (14)	0	1 (5)

*Data collection is on-going in some patients.

Table 3. Treatment-related (possible, probable, definite) non-hematological AEs (if ≥ grade 2 in one patient): number of patients (%)*

AEs, n (%)	Cohort (IMO-2055 dose)				Total (N=20)
	0.08 mg/kg (n=4)	0.16 mg/kg (n=6)	0.32 mg/kg (n=7)	0.48 mg/kg (n=3)	
Diarrhea					
Grade 1/2	1 (25)	2 (33)	1 (14)	2 (67)	6 (30)
Grade 3	1 (25)	0	1 (14)	0	2 (10)
Nausea					
Grade 1/2	1 (25)	1 (17)	2 (29)	1 (33)	5 (25)
Tongue disorder					
Grade 2	0	1 (17)	0	0	1 (5)
Mucosal inflammation					
Grade 2	0	1 (17)	0	0	1 (5)
Weight loss					
Grade 1/2	2 (50)	0	0	0	2 (10)
Hypokalemia					
Grade 1	0	0	0	1 (33)	1 (5)
Grade 3	1 (25)	0	0	0	1 (5)
Hypomagnesemia					
Grade 1/2	1 (25)	1 (17)	0	1 (33)	3 (15)

Table 3. Treatment-related (possible, probable, definite) non-hematological AEs (if ≥ grade 2 in one patient): number of patients (%)* (Continued)

AEs, n (%)	Cohort (IMO-2055 dose)				Total (n=20)
	0.08 mg/kg (n=4)	0.16 mg/kg (n=6)	0.32 mg/kg (n=7)	0.48 mg/kg (n=3)	
Chills					
Grade 1/2	2 (50)	1 (17)	2 (29)	0	5 (25)
Fatigue					
Grade 1/2	2 (50)	2 (33)	1 (14)	1 (33)	6 (30)
Grade 3	0	0	0	1 (33)	1 (5)
Asthenia					
Grade 2	0	1 (17)	0	0	1 (5)
Pollakiuria					
Grade 2	0	0	1 (14)	0	1 (5)
Rash					
Grade 1/2	2 (50)	0	0	0	2 (10)
Acne					
Grade 2	0	0	0	1 (33)	1 (5)
Dermatitis acneiform					
Grade 2	1 (25)	0	0	0	1 (5)
Pyrexia					
Grade 2	0	0	0	1 (33)	1 (5)
Night sweats					
Grade 1/2	1 (25)	1 (17)	0	0	2 (10)
Injection-site pain					
Grade 1/2	0	3 (50)	0	0	3 (15)
Injection-site reaction					
Grade 1/2	2 (25)	3 (50)	3 (43)	1 (33)	9 (45)
Grade 3	0	1 (17)	0	0	1 (5)
Injection-site abscess					
Grade 3	0	1 (17)	0	0	1 (5)
Injection-site infection					
Grade 2	0	1 (17)	0	0	1 (5)

*Data collection is on-going in some patients.

ANTITUMOR ACTIVITY

- Thirteen of the 16 patients enrolled to the dose escalation portion of the study were evaluable for tumor response.
- Reasons for exclusion were: no post-baseline data (died of unrelated causes after 7 days on treatment, n=1), no measurable disease (n=1) and no post-baseline data available (n=1).
- Responses are shown in Table 4. Objective response rate (ORR: CR+PR) was 23% and the clinical benefit rate (CBR: CR+PR+SD) was 85%.

Table 4. Response rate (N=13)

Response	No. of patients	(%)
PR	3	23
SD	8	62
PD	2	15
Objective response rate (CR+PR)	3	23
Clinical benefit rate (CR+PR+SD)	11	85

CONCLUSIONS

- The combination of weekly IMO-2055 administration with daily erlotinib and bevacizumab every 3 weeks demonstrated anti-tumor activity in pretreated patients with advanced/metastatic NSCLC that compares favorably to the reported efficacy of erlotinib plus bevacizumab in a similar patient population.¹³
- Three patients of the 13 evaluable in the dose escalation phase had a PR, giving an ORR of 23%, while an additional 8 patients had SD, giving a CBR of 85%.
- Eight of the 16 patients in the dose escalation phase remained on treatment for at least 18 weeks.
- IMO-2055 was well tolerated at doses up to 0.48 mg/kg/wk (SC on d1, 8, and 15) in combination with erlotinib (PO 150 mg/d) plus bevacizumab (IV 15 mg/kg on d1) q3w.
- DLTs were grade 3 anorexia, dehydration, and facial acneiform rash at 0.16 mg/kg/wk (n=1) and grade 3 fatigue at 0.48 mg/kg/wk (n=1).
- There was a low incidence of related grade 3 AEs and no related grade 4 AEs. The AE profile of IMO-2055 was consistent with that expected from an immunomodulator, including injection site reactions from SC administration.
- The maximum tolerated dose was not reached. It was decided to continue enrollment with IMO-2055 at 0.32 mg/kg/wk based on previous pharmacodynamic data from prior studies^{4,5} and the observation of 1 DLT at 0.48 mg/kg/wk.
- Recruitment of additional patients is continuing at 0.32 mg/kg/wk in the expansion cohort as the anticipated recommended phase 2 dose level for IMO-2055.

REFERENCES

- Yu D et al. Nucleic Acids Res 2002;30:4460-9.
- Agrawal DK et al. Int Immunopharmacol 2004;4:127-38.
- Wang D et al. Int J Oncol 2004;24:901-8.
- Idera [data on file].
- Damiano V et al. Clin Cancer Res 2006;12:577-83.
- Damiano V et al. PNAS 2007;104:12468-73.
- Wang D et al. J Clin Oncol 2006;24(Suppl. 18S) (Abstr 2568).
- Moore DJ et al. J Clin Oncol 2005;23(Suppl. 16S) (Abstr 2503).
- Malik S et al. Poster presented at the 12th World Conference on Lung Cancer, Sep 2-6 2007, Seoul, Korea.
- Tarceva prescribing information. Available at: <http://www.gene.com/gene/products/information/pdf/tarceva-prescribing.pdf>
- Avastin prescribing information. Available at: <http://www.gene.com/gene/products/information/pdf/avastin-prescribing.pdf>
- Genentech press release May 30, 2009.
- Genentech press release October 5, 2008; Roche press release November 14, 2008; Herbst R et al. Poster presented at the International Association for the Study of Lung Cancer conference August 2, 2009.