

Investigation of IMGN901 in  
CD56<sup>+</sup> Solid Tumors:  
Results from a Phase I/II Trial (Study  
001) and a Phase I Trial (Study 002)

Combined Experience in a  
Subset of Patients with  
Small-Cell Lung Cancer (SCLC)

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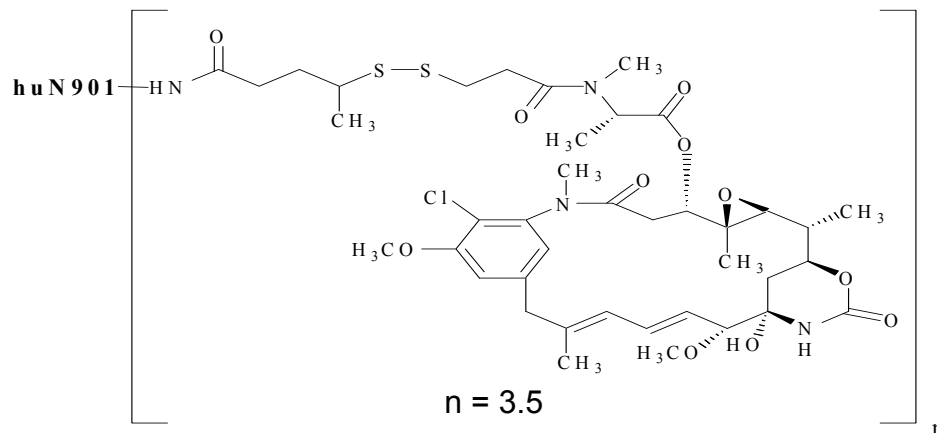
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# Rationale/Background

- IMGN901 is an antibody-drug conjugate (ADC) comprised of the CD56-binding monoclonal antibody, huN901, and the maytansinoid cytotoxic agent, DM1.
- The CD56 antigen is a neural cell adhesion molecule (NCAM) that is expressed on the surface of tumor cells of neuroendocrine origin, including SCLC, carcinoid tumors and Merkel cell carcinomas (MCC). CD56 is expressed on virtually all SCLCs.
- IMGN901 binds with high affinity to CD56 expressed on the surface of tumor cells. Once bound, the conjugate is internalized and the DM1 is released.
- DM1 is an antimetabolic agent that disrupts tubulin polymerization and microtubule assembly (Remillard S *et al.*, 1975, *Science* 189:1002-1005)
- IMGN901 has shown marked anticancer activity in human SCLC xenograft preclinical models (Chari RVJ *et al.*, 2000, *Proc. Am. Assoc. Cancer Res. Abstract* 4405)

# IMGN901 (huN901-DM1; BB-10901)

- huN901 antibody
  - Targets CD56 (NCAM)
  - CD56 is expressed on virtually all SCLCs
- DM1
  - Proprietary maytansinoid derivative
  - Inhibitor of tubulin polymerization; anti-mitotic
  - Attached to huN901 with disulfide linker



## CD56 expression in human tumors based on in house data

### • SCLC

- ✓ 97% (65/67 cases) showed strong uniform cell surface staining

### • Multiple Myeloma

- ✓ 78% (43/55cases) showed strong expression

### • Neuroendocrine Tumors

- ✓ 78% (88/113 cases) showed strong expression
  - Pancreatic: 56% (9/16)
  - Gastrointestinal: 68% (22/32)
  - Typical and atypical carcinoid of lung: 88% (29/33)
  - Large cell neuroendocrine carcinoma of lung: 80% (4/5)

### • Neuroblastoma

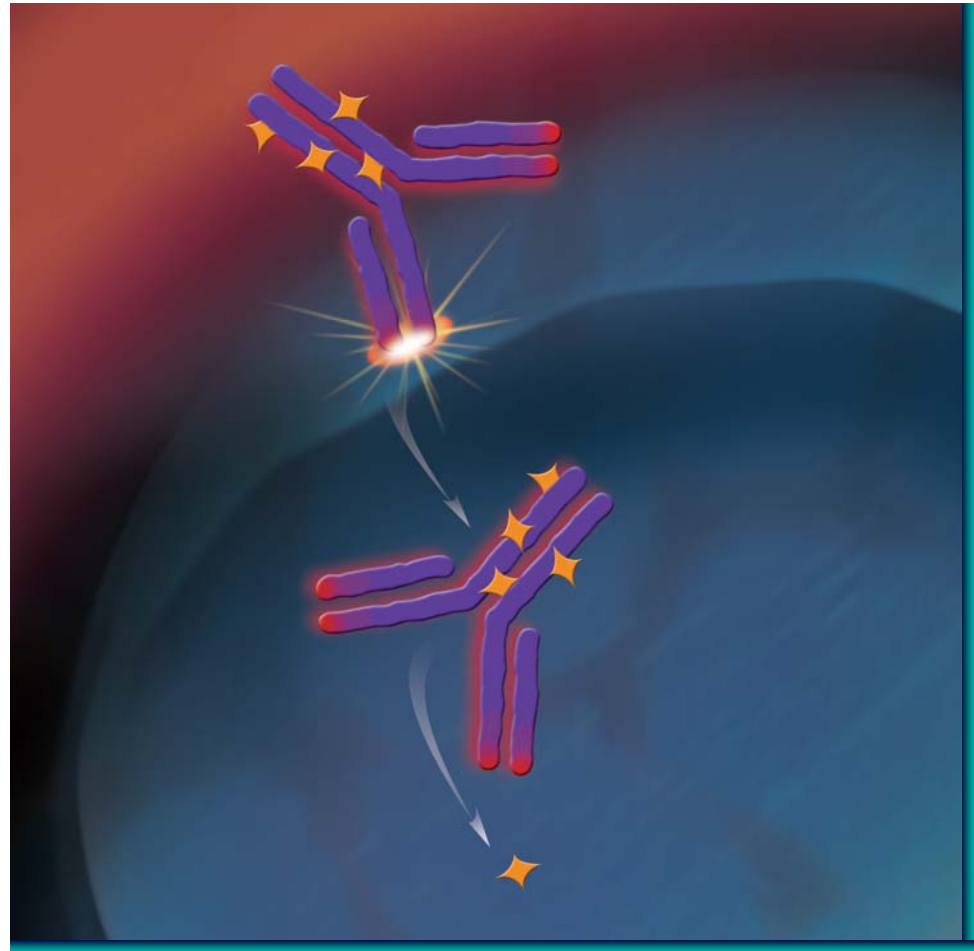
- ✓ 100% (15/15 cases)

### • Other Indications

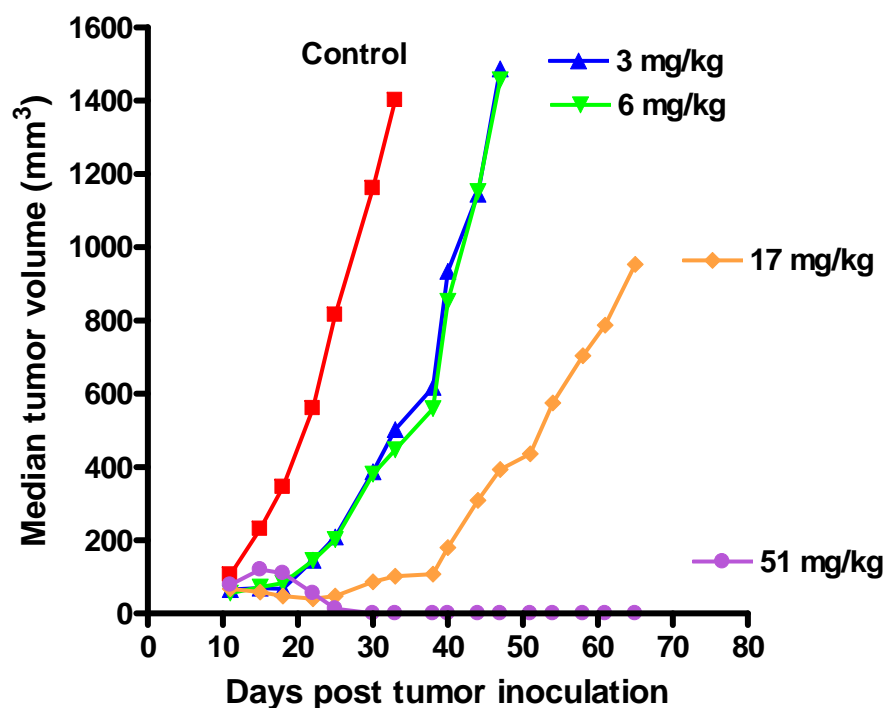
- ✓ CD56<sup>+</sup> leukemia, Wilms' tumor, CD56<sup>+</sup> lymphoma, astrocytoma, rhabdomyosarcoma, schwannoma, osteosarcoma

# How Antibody-Maytansinoid Conjugates Work

1. Bind to targets on the surface of cancer cells
2. Brought into the cell by natural processes
3. Once inside, the maytansinoid agent is freed and able to kill the cancer cell



# IMGN901 demonstrates dose-dependent anti-tumor activity against subcutaneous CD56<sup>+</sup> SW2 SCLC xenografts

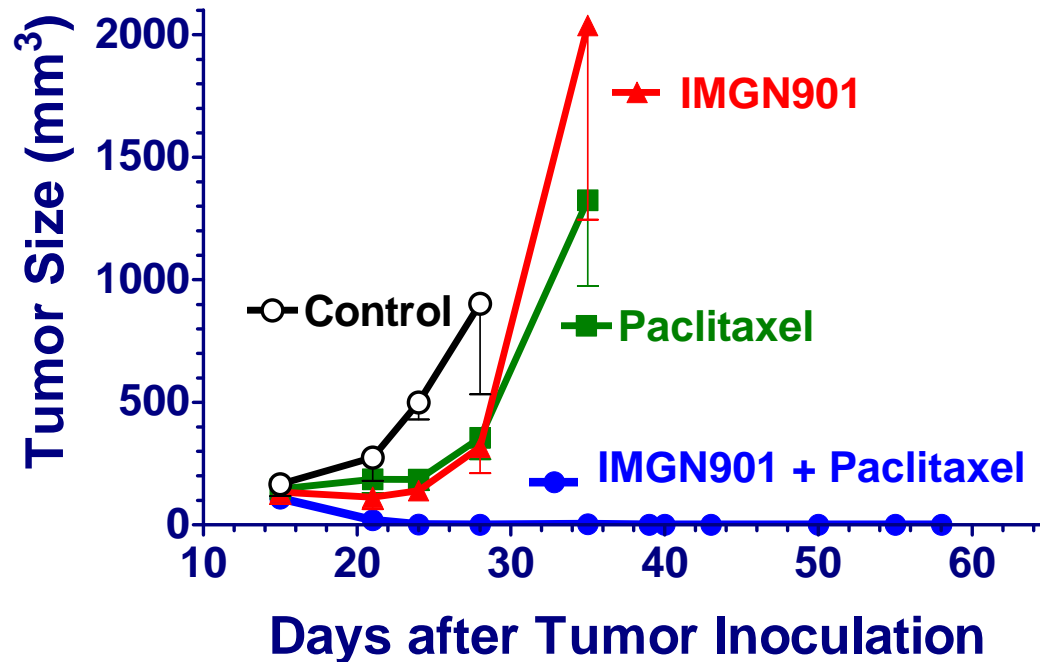


Dose of IMGN901 (mg/kg)	T/C (%)	Tumor-free survivors	Response
3	29	0/6	active
6	29	0/6	active
17	6	3/6	highly active
51	0	5/5	highly active

Single-dose administration  
10 days post inoculation

$$T/C (\%) = \frac{\text{Median volume of treated (T) tumors on day 27}}{\text{Median volume of control (C) tumors on day 27}} \times 100$$

# IMGN901 in combination with paclitaxel is highly active against subcutaneous CD56<sup>+</sup> NCI-N417 SCLC xenografts



IMGN901 - 3.6 mg/kg on days 15, 16, 17, 18, 19  
Paclitaxel - 2 mg/kg on days 15, 17, 19  
Combination at the same doses and schedules

# Objectives and Design: Studies 001 and 002

## Study 002 and the Phase I Portion of Study 001

### Objectives

- Primary – determine safety, tolerability and maximum tolerated dose (MTD)
- Secondary
  - Determine pharmacokinetics
  - Preliminary assessment of efficacy

### Design

- Traditional Phase I dose-escalation design

## The Phase II Portion of Study 001

### Objectives

- Primary – determine efficacy at a dose of 60 mg/m<sup>2</sup>
- Secondary – continue to characterize safety, tolerability and pharmacokinetics

### Design

- Gehan's two-stage design
- Stage 1 required 1 response among the first 14 patients
- Stage 2 increases sample size to 35 patients

# Methods:

## Studies 001 and 002

### Study 001

- IMGN901 administered intravenously weekly for 4 consecutive weeks every 6 weeks
- 1 cycle = 6 weeks
- Protocol permitted up to an additional 4 weeks between each cycle
- Radiologic assessment performed at screening and every 6 weeks

### Study 002

- IMGN901 administered intravenously daily for 3 consecutive days every 3 weeks
- 1 cycle = 3 weeks
- Radiologic assessment performed at screening, after cycles 1, 3, 4 and then at every other cycle

# Combined Patient Population: Studies 001 and 002

Study 001 is closed; Study 002 is ongoing

Total number of patients to date = 113

- 68 SCLC
- 27 Neuroendocrine/Carcinoid
- 6 Merkel Cell Carcinoma
- 12 Other CD56<sup>+</sup> solid tumor
  - 3 non-pulmonary small cell carcinoma
  - 3 sarcoma
  - 1 hallux
  - 1 thyroid
  - 1 lung
  - 1 adrenal
  - 1 NSCLC
  - 1 unknown primary

# Common Patient Eligibility Criteria: Studies 001 and 002

## **INCLUSION CRITERIA**

- Histologically/cytologically proven SCLC or other pulmonary tumors of neuroendocrine origin, including neuroendocrine carcinoma and NSCLC with neuroendocrine features, non-pulmonary small cell carcinoma, metastatic carcinoid tumor, or other CD56<sup>+</sup> solid tumors
- Tumors other than SCLC require confirmation of CD56 expression prior to enrollment
- No more than 3 prior therapies
- Measurable disease
- Predicted survival of at least 3 months
- ECOG performance status 0-2
- ANC  $\geq 1.5 \times 10^9/l$ , hemoglobin  $\geq 9$  g/dl, platelets  $\geq 100 \times 10^9/l$
- Creatinine  $\leq 1.5 \times$  ULN, AST/ALT  $\leq 3 \times$  ULN ( $\leq 5 \times$  ULN in pts with liver metastases)

## **EXCLUSION CRITERIA**

- Chemotherapy, other investigational agents or radiotherapy within 4 weeks prior to study entry
- Known CNS metastases
- Previous monoclonal antibody therapy
- History of multiple sclerosis or other demyelinating disease, Eaton-Lambert syndrome
- History of pancreatitis
- Current active varicella-zoster virus or cytomegalovirus infection or history of recurrent infection with these viruses

**Table 1. Baseline Demographics and Disease Characteristics: Studies 001 and 002**

	001 Phase I		001 Phase II		002 study	
	All n=32	SCLC n=19	All n=32	SCLC n=29	All n=49	SCLC n=20
<b>Average Age in Years</b>	60	63	60	62	53	57
<b>Sex (Male/Female)</b>	22/10	14/5	19/13	18/11	28/21	10/10
<b>Race</b>	27 White 3 Black 2 Hispanic	16 White 2 Black 1 Hispanic	28 White 1 Black 3 Hispanic	26 White 1 Black 2 Hispanic	47 White 2 Black	20 White
<b>ECOG Performance Status at Screening*</b>						
0	2	0	7	6	9	3
1	26	18	24	23	33	14
2	4	1	1	0	5	3
<b>Prior Chemotherapy Regimens</b>						
None	4	0	0	0	0	0
1	10	7	19	17	20	7
2	10	8	11	10	23	10
>2	8	4	2	2	6	3
<b>Prior Radiotherapy</b>						
None	15	8	11	10	18	2
At least 1	17	11	21	19	31	18
<b>Relapsed/Refractory/Neither</b>	10/17/5	8/11/0	32/0/0	29/0/0	24/25/0	14/6/0

\*The ECOG performance status is not available for 2 patients in Study 002

**Table 2. Selected Treatment-Related Adverse Events\* (AEs)  
in All Tumor Types in Studies 001 and 002 (n=113)**

	Number of Patients with AE			
	Grade 1	Grade 2	Grade 3	Grade 4
<b>Headache**</b>	15	15	5	2
<b>Meningitis non-infective**</b>			3	1
<b>Nausea</b>	22	7	4	
<b>Vomiting</b>	6	8	5	
<b>Myocardial Infarction</b>				1
<b>Diarrhea</b>	7	2		
<b>Fatigue</b>	13	8	4	1
<b>Neuropathy</b>	24	5	3	
<b>Pancreatitis</b>		1	1	1

\*Considered at least possibly, probably, or definitely related to study drug.

\*\*After implementation of a slowed infusion rate and routine steroid prophylaxis prior to treatment, grade 3 / 4 headache and meningitis-like symptoms have not been reported.

**Table 3. All Treatment-Related Serious AEs (SAEs) in All Tumor Types in Studies 001 and 002 (n=113)**

	Number of Patients with SAE		
	Possibly Related	Probably Related	Definitely Related
Abdominal Pain	1 Gr 2		
Confusional State		1 Gr 3	
Constipation	1 Gr 2; 1 Gr 3		
Dehydration	1 Gr 3		
Dizziness	1 Gr 2		
Encephalopathy		1 Gr 3	
Fatigue/Lethargy	1 Gr 3	1 Gr 4	
Headache	1 Gr 1	1 Gr 4	2 Gr 3; 1 Gr 4
Hyponatraemia	1 Gr 3		
Hypotension	1 Gr 3		
Inappropriate Antidiuretic Hormone Secretion	1 Gr 3		
Meningitis Non-infective/Meningism	2 Gr 3	1 Gr 3	
Myocardial Infarction	1 Gr 4		
Nausea			2 Gr 3
Pain	3 Gr 3		
Pancreatitis	1 Gr 2; 1 Gr 3; 1 Gr 4		
Peripheral Ischaemia	1 Gr 3		
Neuropathy/Hyperaesthesia			1 Gr 3
Popliteal Stenosis	1 Gr 3		
Pyrexia	1 Gr 1		
Retroperitoneal Haemorrhage/Multi-organ Failure*	1 Gr 4; 1 unknown		
Tachycardia	1 Gr 2		
Vomiting	1 Gr 2		2 Gr 3

\* AE terms were grouped together as events occurred in the same patient at the same time.

**Table 4. Response to Treatment SCLC Patients (n=68): Partial response (PR) and Stable Disease (SD) in Studies 001/ 002**

Study	Patient	Dose (mg/m <sup>2</sup> )	Lines of therapies	Response	Cycles	TTP <sup>†</sup> (Days)	TTP <sup>†</sup> (Weeks)
001	114	60	1	SD	1	57*	8.14*
001	211	67.5	3	SD	2	77	11.00
001	101	5	2	SD	2	79	11.29
001	1201	60	1	SD	2	79	11.29
001	1101	60	3	SD	1	80	11.43
001	901	60	2	SD	2	81	11.57
001	122	67.5	1	SD	2	83	11.86
001	215	60	2	SD	1	89*	12.71*
001	405	60	2	SD	1	90*	12.86*
001	125	60	1	SD	2	96	13.71
001	302	60	1	SD	2	105	15.00
001	1001	60	1	SD	3	132	18.86
001	402	60	1	SD	4	168	24.00
001	127	60	1	PR	5	169	24.14
002	509	75	2	SD	2	26	3.71
002	308	48	2	SD	2	41**	5.86**
002	504	75	2	SD	2	45	6.43
002	401	8	2	SD	3	57	8.14
002	304	16	1	SD	3	58	8.29
002	412	75	2	uPR ††	3	58	8.29
002	415	75	2	SD	3	90*	12.86*
002	405	24	1	SD	3	92*	13.14*
002	207	16	3	SD	6	138*	19.71*

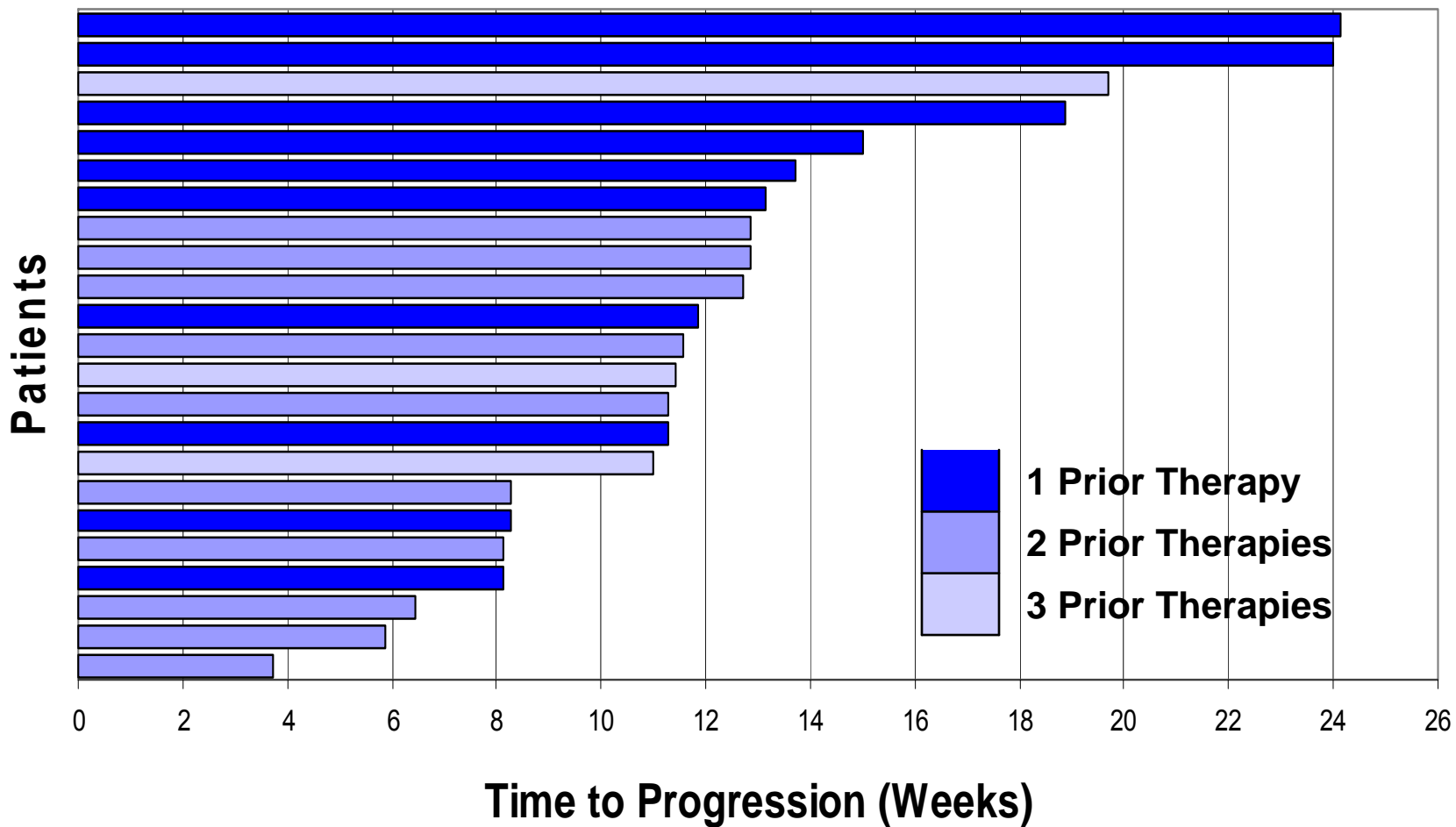
† Time to Progression (TTP) †† Unconfirmed PR

\* TTP was estimated based on the start of treatment to the last study visit.

\*\* TTP was estimated based on the start of treatment to clinical progression on study.

# Response to Treatment in Patients with SCLC (n=68)

PR and SD in Studies 001 and 002



# Summary of Efficacy Data: SCLC (n = 68) Studies 001 and 002

## Objective Responses

- One confirmed PR in second-line setting without evidence of progressive disease for 169 days (24 weeks)
- One unconfirmed PR as third line treatment without evidence of progressive disease (PD) for 58 days (8.3 weeks)

## Stable Disease

- 15 patients who received IMG901 as  $\geq$  2<sup>nd</sup> line therapy had estimated TTP ranging from 77 to 168 days. This compares favorably to median TTP of 13.3 weeks (93 days) seen with topotecan as 2<sup>nd</sup> line treatment for SCLC (von Pawel *et al.*, 2009, *JCO*, 17: 658-667).
- Of these 15 patients, 8 patients received IMG901 as  $\geq$  3<sup>rd</sup>-line treatment with estimated TTP ranging from 77 to 138 days.

## Estimated Clinical Benefit Rate (CBR) = 25% (17 of 68 patients)

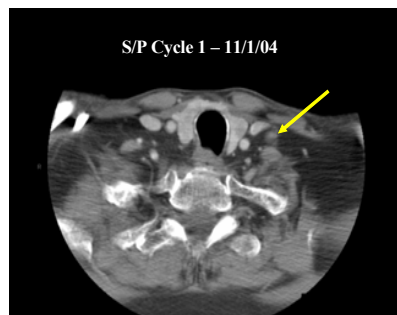
- CBR = PR + SD (defined as non-progression for at least 77 days)
- Represents second and  $\geq$  third-line patient populations

## Case Report: Patient 0127 in Study 001

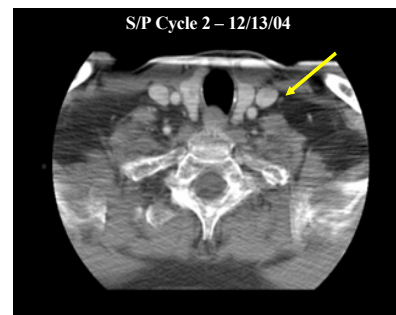
- 61-year old male diagnosed limited stage SCLC Jan 2004
- Had received concurrent chemotherapy/radiotherapy (XRT) with cisplatin, etoposide, and topotecan concurrent with 45 Gy XRT to primary tumor and mediastinum → complete response May 2004
- Had received prophylactic cranial XRT
- PET scan Aug 2004: disease progression left supraclavicular fossa
- Treatment with IMGN901
- Achieved a PR after first cycle of IMGN901: 65% reduction in tumor volume after cycle 1, 78% reduction after cycle 2, and 91% reduction after cycle 3
- PD after cycle 4



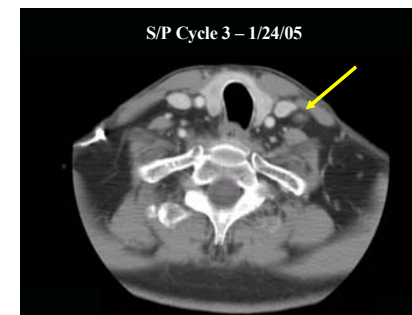
17 SEP 04  
**Baseline**



1 NOV 04  
**Post Cycle 1**



13 DEC 04  
**Post Cycle 2**



24 JAN 05  
**Post Cycle 3**

**Table 5. Response to Treatment in Patients with Other Tumor Types (n=45):  
Complete Response (CR), PR and SD in Studies 001 and 002**

Study	Patient	Diagnosis	Dose (mg/m <sup>2</sup> )	Lines of therapies	Response	Cycles	TTP (Days)	TTP (Weeks)
001	303	SMALL CELL CERVICAL NEUROENDOCRINE CANCER	60	2	uPR ††	1	63	9.00
001	108	METASTATIC CARCINOID TUMOUR: PRIMARY SITE UNKNOWN	20	0	SD	3	125	17.86
001	117	METASTATIC CARCINOID TUMOR: LUNG - RIGHT LOWER LOBE	60	0	SD	3	136*	19.43*
001	204	METASTATIC CARCINOID TUMOUR: RECTUM (RECTAL POLYP)	20	1	SD	4	160	22.86
001	205	NEUROENDOCRINE CARCINOMA: PANCREAS	40	0	SD	4	164	23.43
001	123	METASTATIC CARCINOID TUMOUR: RIGHT LUNG	60	3	SD	4	195*	27.86*
001	209	NEUROENDOCRINE CARCINOMA: UNKNOWN PRIMARY	75	2	SD	5	213*	30.43*
002	503	NEUROENDOCRINE CARCINOMA: ADRENOCORTICAL	60	1	SD	1	16**	2.29**
002	402	OTHER CD56+ SOLID TUMOUR: RIGHT HALLUX	16	2	SD	2	21**	3.00**
002	502	NEUROENDOCRINE CARCINOMA: GALL BLADDER FUNDUS	60	1	SD	1	23**	3.29**
002	411	OTHER CD56+ SOLID TUMOUR - UNKNOWN PRIMARY	60	2	SD	3	49**	7.00**
002	302	NEUROENDOCRINE CARCINOMA: LUNG RIGHT UPPER LOBE	16	1	SD	2	57	8.14
002	101	NEUROENDOCRINE CARCINOMA: PRIMITIVE NEUROECTODERMAL TUMOURS L THORACIC CAVITY	4	1	SD	3	59	8.43
002	403	OTHER CD56+ SOLID TUMOUR: RIGHT THYROID	16	1	SD	3	59	8.43
002	307	NEUROENDOCRINE CARCINOMA: RIGHT LUNG AND RIGHT HILAR LYMPH NODE	48	3	SD	3	63**	9.00**
002	505	NEUROENDOCRINE CARCINOMA: SCALP	75	3	SD	4	79*	11.29*
002	501	NEUROENDOCRINE CARCINOMA: LUNG	48	2	SD	2	98*	14.00*
002	417	MERKEL CELL RIGHT LEG	60	1	PR	1	108***	15.43***
002	309	METASTATIC CARCINOID TUMOUR: RIGHT HILAR LUNG	75	1	SD	5	109	15.57
002	409	NEUROENDOCRINE CARCINOMA: RIGHT LUNG	48	1	SD	5	115	16.43
002	303	OTHER CD56+ SOLID TUMOUR: LUNG	16	2	SD	5	115	16.43
002	210	METASTATIC CARCINOID TUMOUR: ROOT OF MESENTRY	36	1	SD	6	124*	17.71*
002	413	OTHER CD56+ SOLID TUMOUR: RIGHT FOOT	75	1	SD	6	131*	18.71*
002	212	NEUROENDOCRINE CARCINOMA: RIGHT SIDE OF ABDOMEN	60	2	SD	6	132*	18.86*
002	406	MERKEL CELL TUMOUR, RIGHT CHEEK	36	2	CR	6	1551***	221.57***

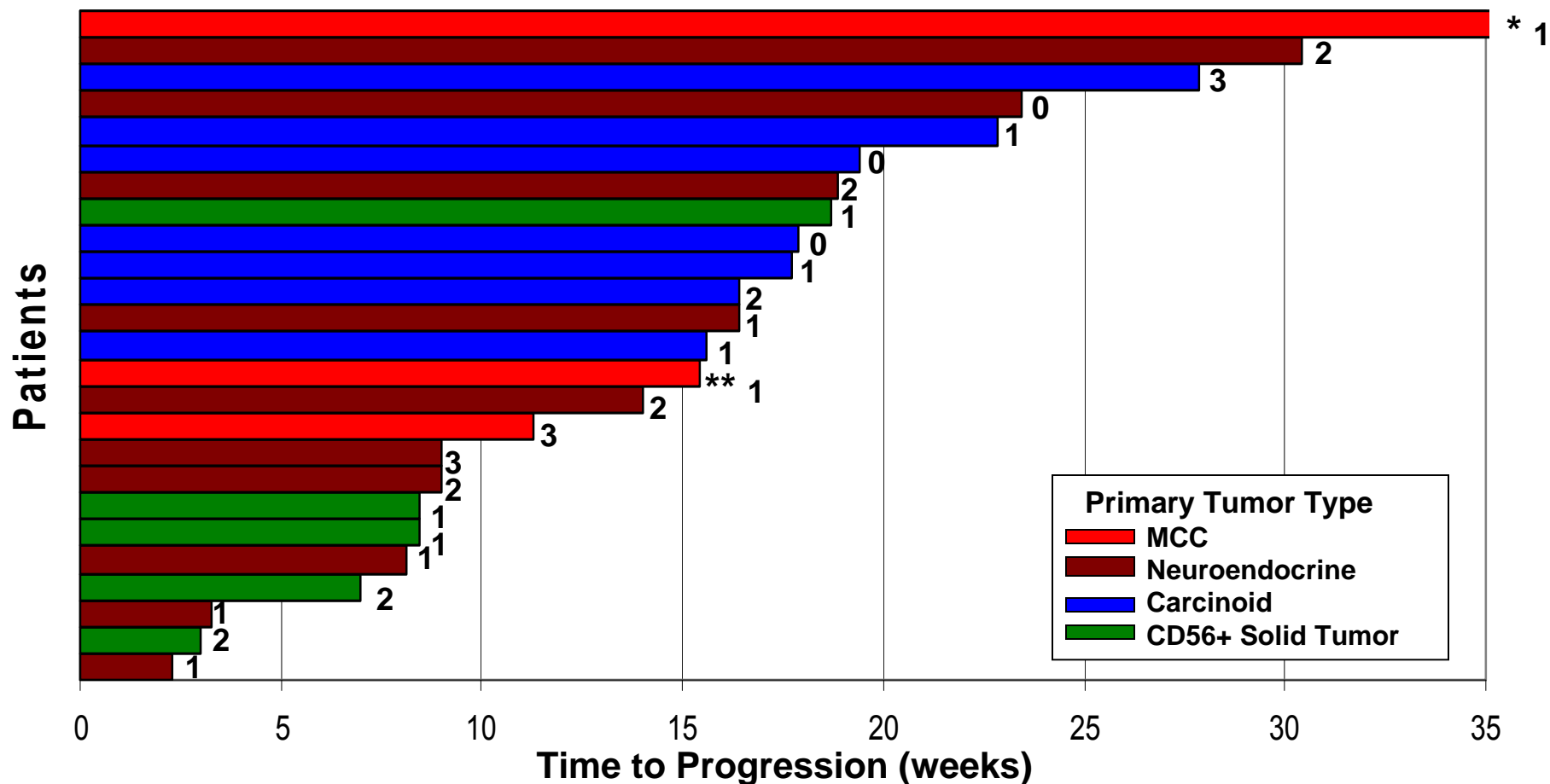
\* TTP was estimated based on the start of treatment to the last study visit.

† † Unconfirmed PR

\*\* TTP was estimated based on the start of treatment to clinical progression on study.

\*\*\* TTP was estimated based on the start of treatment to a post study investigator assessment

## Response to Treatment in Patients with Other CD56+ Tumor Types (n=45) CR, PR, and SD: Studies 001 and 002



**Note:** Numbers to the right of each bar represent the number of prior therapies the patient received.

\*Patient with MCC alive with no evidence of recurrence at > 4 years

\*\*Patient continues to derive clinical benefit > 15 weeks after one cycle of treatment

# Supportive Data: IMGN901 Efficacy in MCC (n=6) Study 002

- 1 CR
  - Patient had multiple prior recurrences and had PD within ~ 1 month of adjuvant treatment with surgery, radiation (XRT), and chemotherapy
  - Treated with IMGN901 at 36 mg/m<sup>2</sup> x 6 cycles
  - PR observed after 1<sup>st</sup> cycle and CR observed by end of 3<sup>rd</sup> cycle
  - Has been progression free > 4 years
- 1 PR
  - Patient had PD within ~ 1 month of previous chemotherapy regimen
  - Treated with IMGN901 at 60 mg/m<sup>2</sup> x 1 cycle
  - IMGN901 discontinued after 1 cycle – patient developed Reversible Posterior Leukencephalopathy Syndrome
  - Confirmed by CT scan 9 weeks after initial CT scan documenting PR.
- 1 SD
  - Patient with bone metastases who had received 3 prior chemotherapy regimens and had developed PD within 2 months of most recent regimen
  - Treated with IMGN901 at 75 mg/m<sup>2</sup> x 4 cycles (79 days)
- 3 PD after 1 cycle of IMGN901

# Supportive Data: IMGN901 Efficacy in Neuroendocrine and Carcinoid (n=27) Studies 001 and 002

## Objective Response

1 unconfirmed PR as 3<sup>rd</sup>-line therapy in a patient with small cell cervical neuroendocrine carcinoma treated at a dose of 60 mg/m<sup>2</sup>

## Stable Disease

13 of 26 patients experienced durable SD

- Estimated TTP ranged from ~100 to >200 days
- Number of prior chemotherapy regimens:
  - 0 regimens: 3 patients, one each with carcinoid – lung, carcinoid – unknown primary, and pancreatic neuroendocrine
  - 1 regimen: 5 patients
  - 2 regimens: 4 patients
  - 3 regimens: 1 patient

# IMGN901 Pharmacokinetic Parameters

## Studies 001 and 002

Study 001						
Dose mg/m <sup>2</sup>	N of Patients	C <sub>max</sub> (µg/mL)	t <sub>½</sub> (H)	AUC <sub>0-∞</sub> (µg.h/mL)	Cl (mL/h/m <sup>2</sup> )	V <sub>ss</sub> (mL/m <sup>2</sup> )
5	4	1.5 (0.5)	6.1 (0.9)	15.8 (5.6)	346 (120)	3014 (551)
10	3	4.0 (1.4)	6.1 (1.6)	31.9 (3.9)	317 (37.3)	2674 (873)
20	4	10.4 (0.6)	17.6 (7.0)	137 (39.5)	160 (55.2)	3596 (519)
40	4	26.5 (11.0)	21.0 (3.4)	556 (198)	78.4 (24.3)	1877 (523)
60	24	49.4 (32.6)	16.6 (4.8)	1329 (1163)	70.3 (37.1)	1534 (786)
67.5	4	38.1 (7.9)	20.4 (2.5)	992 (307)	75.9 (33.7)	1724 (915)
75	4	46.9 (7.5)	20.3 (2.9)	931 (220)	84.2 (20.5)	2245 (483)
Study 002						
4	4	3.6 (2.3)	8.4 (4.2)	39.6 (29.4)	145 (87.8)	1181 (533)
8	3	6.8 (1.9)	14.4 (3.9)	132 (84.9)	78.9 (44.4)	1307 (559)
16	6	16.4 (6.8)	19.2 (4.8)	347 (114)	49.6 (12.9)	1195 (302)
24	3	38.6 (18.4)	12.1 (4.9)	618 (203)	41.4 (11.6)	534 (305)
36	4	36.2 (10.6)	17.8 (2.1)	745 (152)	50.2 (12.2)	1095 (350)
48	6	69.4 (34.3)	20.3 (3.7)	1323 (345)	38.9 (12.5)	899 (306)
60	4	73.5 (30.9)	26.8 (12.9)	3067 (2218)	33.6 (27.8)	824 (433)
75	9	83.4 (40.1)	20.9 (7.7)	3670 (2501)	26.8 (13.6)	988 (561)
<p>AUC<sub>0-∞</sub>: area under serum concentration <i>versus</i> time curve; V<sub>ss</sub>: apparent volume of distribution; C<sub>max</sub>: maximum serum concentration, t<sub>½</sub>: half life, Cl: clearance. Results shown as mean (± standard deviation) for patients with evaluable data. *Data for cycle 1 dose 1 for one patient at 112 mg/m<sup>2</sup> (pt. 218) was excluded from PK calculations due to unexpectedly low IMGN901 plasma levels. IMGN901 levels for later doses in this patient (Cycle 1 Dose 1, Cycle 5 Dose 1) were within the expected range.</p>						

# Conclusions

- Encouraging, initial activity has been observed with IMG901 in patients with pretreated, relapsed or refractory SCLC. Activity has been noted in both the 2<sup>nd</sup>- and  $\geq$  3<sup>rd</sup>-line treatment settings.
- Based on shared morphologic characteristics and clinical behavior, SCLC and MCC are treated similarly. The activity noted in MCC is supportive of the activity of IMG901 in SCLC.
- The favorable safety profile seen in total population of both studies was maintained in the subset of patients with SCLC.
- The tolerability profile seen with IMG901 is supportive of exploring its use in combination with established chemotherapy regimens.
- The plasma half-life of IMG901 is more extended at higher doses. This may be due to the saturation of readily accessible CD56<sup>+</sup> cells (e.g. NK cells) and/or soluble CD56, which is known to be elevated in many patients with SCLC.
- Additional clinical investigations are currently under discussion.