

# An open label phase I study of ABR-217620, a fusion protein of the 5T4 antibody moiety and an engineered superantigen, in patients with non-small cell lung, renal or pancreatic cancer

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## INTRODUCTION

ABR-217620 (naptumomab estafenatox) is a recombinant fusion protein that consists of an anti-5T4 Fab moiety genetically fused to the engineered superantigen variant SEAVE-120. This fusion protein is a 2nd generation tumor targeted superantigen based on the previously described ABR-214936 (anatumomab mafatenotox). ABR-217620 has reduced antigenicity and toxicity in preclinical studies. The 5T4 antigen is expressed on more than 95% of tumors from patients with non-small cell lung (NSCLC), renal cell (RCC) and pancreatic cancer (PC). In clinical PET studies<sup>124</sup>-labeled ABR-217620 has been shown to localize to 5T4 positive tumors.

Figure 1 Mechanism of action for ABR-217620

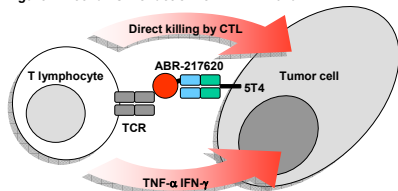
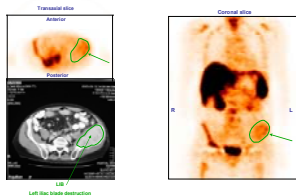


Figure 2 Tumor localization study using <sup>124</sup>I labeled ABR-217620 in a patient with a RCC metastasis



## MATERIALS AND METHODS

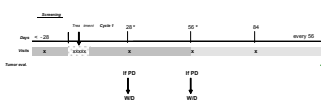
**Primary Endpoint:** Determine the MTD of ABR-217620 as a function of pre-treatment anti-SEA/E-120 levels in patients with advanced non-small cell lung cancer, renal clear cell carcinoma or pancreatic cancer.

**Secondary Endpoints:** Determine the safety profile, pharmacokinetic parameters of ABR-217620, immunological response to the treatment, objective tumor response, time to progression and survival.

### Main Inclusion Criteria:

1. Patients with NSCLC, RCC or PC refractory to currently available standard therapies. Patients must have received (or declined) at least one standard regimen for advanced/metastatic disease.
2. ECOG performance status of 0 or 1.
3. Adequate bone marrow function (absolute neutrophil count  $\geq 1500/\text{mm}^3$ , platelets  $\geq 100,000/\text{mm}^3$ , hemoglobin  $\geq 10 \text{ g/dL}$ ); renal function (creatinine  $\leq 1.5 \times$  upper limit of normal) and hepatic function (bilirubin  $\leq 2 \times$  upper limit of normal, and SGOT and SGPT  $\leq 2.5 \times$  upper limit of normal).

Figure 3 Study treatment and follow up scheme



ABR-217620 is given as a 5 min bolus injection once daily for 5 consecutive days. Patients with SD or response may be offered additional cycles. Dose escalation has been performed using a Bayesian model starting at 0.5  $\mu\text{g/kg/day}$ .

## RESULTS

### Patient Characteristics

Disease	Number of patients	Performance status	Age	Previous therapies*
NSCLC	19 (8M, 11F)	ECOG 0 N=5 ECOG 1 N=14	39-69 years	First line N=1 Second line N=5 Third line N=7 Fourth / later N=6
RCC	10 (6M, 4F)	ECOG 0 N=8 ECOG 1 N=2	39-71 years	First line N=0 Second line N=6 Third line N=4
PC	6 (1M, 5F)	ECOG 0 N=4 ECOG 1 N=2	37-61 years	First line N=1 Second line N=4 Third or later N=1

\*NSCLC and PC: chemotherapy; RCC: immunotherapy

### Safety

35 patients have been treated (19 NSCLC, 10 RCC, 6 PC). 5 patients had DLT at doses between 20 and 28  $\mu\text{g/kg/day}$ . Based on the experience with ABR-214936, these side effects were expected, but the MTD of ABR-217620 is ~ 200 times higher. The side effects resolved quickly.

Disease	Doses ( $\mu\text{g/kg}$ )	Number of patients	DLT	Number of cycles	Typical AE-s (product related)
NSCLC	0.5 - 22.21	19 (8M, 11F)	No	1 cycle: 18 2 cycles: 1	Fever, Nausea, Vomiting, Hypotension
RCC	8.75 - 27.38	10 (6M, 4F)	4 (20, 19-27, 38 $\mu\text{g/kg}$ )	1 cycle: 7 2 cycles: 2 3 cycles: 1	Fever, Nausea, Vomiting, Hypotension
PC	4.92 - 27.38	6 (1M, 5F)	1 (27.38 $\mu\text{g/kg}$ )	1 cycle: 4 2 cycles: 2	Fever, Nausea, Vomiting, Hypotension

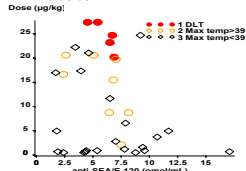
### Dose limiting toxicities

- 02-008** (27.38  $\mu\text{g/kg}$ ): fever of 40.8°C 3 h after injection (grade 3) and blood pressure of 99/47 (resolved with additional intravenous fluid). The patient's general condition was stable despite a short period of dyspnoea and  $\text{O}_2$  of 80% (treated with supplemental oxygen).
- 02-012** (27.38  $\mu\text{g/kg}$ ) hypotension (97/59 grade 2) and increased liver enzymes after injection 1 (liver toxicity grade 3). Treatment was withheld for 1 day but liver enzymes remained increased.
- 03-001** (23.21  $\mu\text{g/kg}$ ): fever of 40.1°C 1½ h after injection (grade 3) and hypotension and tachycardia with a pulse rate up to 120 (resolved with additional intravenous fluid). The patient also suffered from profusion of diarrhea and vomiting (grade 2).
- 03-005** (24.70  $\mu\text{g/kg}$ ): hypotension 6 h after drug administration day 1 and 2. This had responded each day to vigorous IV fluids but was still low the morning at day 3 (grade 3).
- 03-006** (20.19  $\mu\text{g/kg}$ ): Immediately after the last dose (day 5) the patient experienced severe hypotension (grade 4) and renal failure (grade 2).

### Influence of baseline antibodies

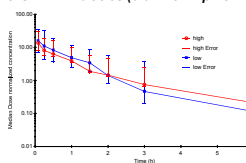
Dosing of previous tumor targeted superantigen compounds was based on levels of preformed anti-SEA/E-120 antibodies. No correlation between the levels of preformed antibodies and MTD was observed for the first cycle of ABR-217620 therapy.

Figure 4 Doses and outcomes for all patients as a function of anti-SEA/E-120 titres



PK analysis supports a minimal influence of anti-SEA/E-120 on MTD. Median normalized plasma levels of ABR-217620 from patients with low (N=7) or high titres (N=7) of anti-SEA/E-120 were analyzed. Only minor differences are observed in the PK properties between the groups.

Figure 5 Plasma concentration time profile of ABR-217620 at treatment day 1 in patients with low (1.72 - 5.43 pmol/ml) or high anti-SEA/E-120 titres (6.51 - 9.22 pmol/ml)



### Immunology

**Cytokines**  
ABR-217620 infusion leads to a dose dependent systemic increase of cytokines including IL-2 and IFN- $\gamma$ .

Figure 6 IL-2(3h) vs Dose Day 1 and 2 and IFN- $\gamma$ (3h) vs Dose Day 1 and 2

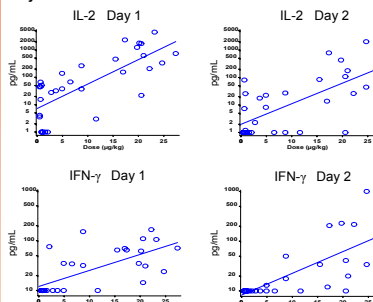
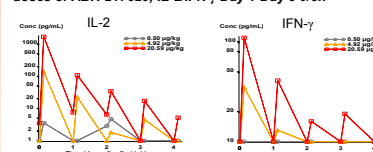


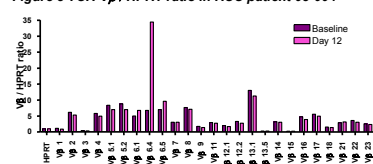
Figure 7 3 patients receiving low, intermediate and high doses of ABR-217620; IL-2/IFN- $\gamma$  Day 1-Day 5 0/3h



### Selective T cell expansion

ABR-217620 treatment leads to expansion of the superantigen reactive T cell population (V $\beta$ 6.4 expressing T cells; approximately 5% of all T cells). The results are presented as a quantitative ratio of TCR-V $\beta$  cDNA copies and HPRT (Hypoxanthine-guanine phosphoribosyltransferase; house-keeping gene) cDNA copies. Samples from 6 patients treated at doses around 20  $\mu\text{g/kg}$  were analyzed.

Figure 8 TCR-V $\beta$ /HPRT ratio in RCC patient 03-004



The table shows the fold increase in V $\beta$  6.4 from baseline to day 12 (ratio day 12/baseline) in the 6 patients analyzed

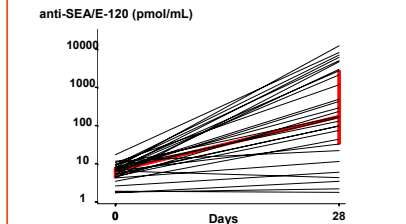
Patient (Dose $\mu\text{g/kg}$ )	01-021 (22.21)	02-006 (20.59)	02-008 (27.38)	03-001 (23.21)	03-002 (17.34)	03-004 (21.84)
V $\beta$ 6.4	4.12	3.11	3.44	2.49	5.48	5.13
Control V $\beta$ †	0.38-0.79	0.54-0.88	0.58-1.07	0.76-1.27	0.58-1.58	0.80-1.37
HPRT	1.00	1.00	1.00	1.00	1.00	1.00

\*Analysis of V $\beta$  1, 2, 3, 4, 5.1, 5.2, 6.1, 6.5, 7, 8, 9, 11, 12.1, 12.2, 13.1, 13.5, 14, 15, 16, 17, 18, 21, 22, 23, 24

### Immunogenicity

Anti-SEA/E-120 before and 28 days after first dose (median and quartiles shown in red). There was no or a moderate increase in anti-SEA/E-120 titres in approximately 60% of the patients. HAMA levels were generally low.

Figure 9 Individual anti-SEA/E-120 titres before and 28 days after ABR-217620 therapy



### CT scan

Efficacy was evaluated by CT scan at day 56. 4/17 (24%) of patients with NSCLC and 2/5 (40%) of patients with RCC had SD.

## CONCLUSION

ABR-217620 treatment had predicted, manageable side effects with fever, hypotension, liver toxicity and nausea being dose limiting toxicities. Treatment with ABR-217620 resulted in a restricted systemic activation of the immune system. Formal efficacy data can obviously not be concluded, but will be evaluated in phase II trials in RCC and NSCLC as combination with docetaxel. The phase I study is still ongoing to refine the estimated MTD.