



ALPHAMAB


## R&amp;D Report

Title: Anti-tumor efficacy of KN035 on  
NOD-SCID xenograft of mixed  
A375-hPDL1/human PBMC

Report#: RDR-KN035-PD-2015-015


Rev#: 01

<i>Rongmei Yan</i>	<i>pharmacology Dept.</i> <i>Assistant Scientist</i>	<i>2016.07.11</i>
Drafted by	Department and position	Date
<i>Dongyue Cao</i>	<i>Pharmacology Dept.</i> <i>Assistant Scientist</i>	<i>2016.07.11</i>
Reviewed by	Department and position	Date
<i>Pilin Wang</i>	<i>pharmacology Dept.</i> <i>Senior Scientist</i>	<i>2016.07.11</i>
Approved by	Department and position	Date

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## Revision history


Rev #	Date	Section(s)	Description of Revision	Reason for Revision
01	See Title Page	N/A	N/A	N/A

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## Abstract


KN035 is a humanized single domain antibody targeting human PD-L1, which does not bind to mouse PD-L1. The anti-tumor efficacy of the drug KN035 depends on immune cells activation. So here we established a xenograft tumor model, by subcutaneous inoculation of mixed human tumor cells and PBMCs into immune-deficient NOD-SCID mice, to directly evaluate the anti-tumor efficacy of humanized antibody drug.

In this study, human melanoma cell line A375 which was stable-transfected with human PD-L1 (A375-hPD-L1), were mixed with human PBMCs as 4:1, and then were subcutaneously inoculated to NOD-SCID mice. Four hours later, the mice received KN035 by i.p. injection with different doses (0.1, 0.3, 1, 3, 10mg/kg, Q1W for four weeks) followed by the antitumor effects evaluation. The results showed that on the A375-hPDL1/human PBMC-NOD/SCID xenograft model KN035 had significant antitumor effect in the doses of 0.1mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg and 10 mg/kg. Furthermore, it did not show an obvious dose-dependent effect, which was similar to the reports by Medimmune.


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## 1. PURPOSE

Study the antitumor effect of different doses of KN035 using an A375-hPDL1/human PBMC-NOD/SCID mice xenograft model, in which A375-hPDL1 and human PBMCs mixture was inoculated subcutaneously to NOD-SCID mice.

## 2 Test substance information

Substance	Lot. No.	Manufacturer	Storage
KN035	141230-150205	Alphamab Co. Ltd	2-8°C

## 3 Test substance preparation

Substance: KN035 10.416mg/mL

Solvent: PBS

Gradient dilution method:

KN035 2.5mg/mL: Add KN035 (10.416mg/mL) 0.276mL to 0.876mL PBS, mix well;

KN035 0.75mg/mL: Add KN035 (2.5mg/mL) 0.352mL to 0.821mL PBS, mix well;

KN035 0.25mg/mL: Add KN035 (0.75 mg/mL) 0.373mL to 0.747mL PBS, mix well;

KN035 0.075mg/mL: Add KN035 (0.25mg/mL) 0.320mL to 0.747mL PBS, mix well;

KN035 0.025mg/mL: Add KN035 (0.075mg/mL) 0.267mL to 0.533mL PBS, mix well.


## 4 Animal housing

### 4.1 Animal

Strain: NOD-SCID mouse

Grade: SPF

Supplier: Vital River Laboratory Animal Technology Co. Ltd.

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Animal Certificate Number: 11400700084956

Age (at the beginning): 6-8 weeks

Body weight (at the beginning): 18-22 g

Amount and Gender: 36 females, 6 mice/group

Animal housing: Standard operating procedure.

## 4.2 Food and Water

Animal food was supplied by Kangmaibo (Su Zhou) Technology Inc. Animals had free access to food and autoclaved water.

## 4.3 Environment and Acclimation

Experiments were performed in the SPF grade Animal Facility (KangMaiBo, Co. Ltd.) with the environment of temperature  $23\pm 2^{\circ}\text{C}$ , humidity 40-70% and 12:12-hours light: dark cycle. Animals were housed before the experiment to acclimate to the environment.

## 4.4 Animal selection and fasting


Animals that were health and acclimate to the environment were selected for the experiments. The mice should be free access to regular food and autoclaved water.

# 5 Experiment

## 5.1 Cell culture

### 5.1.1 A375-hPDL1 culture

A375-hPDL1 melanoma cell line was provided by DingFu Target, Inc. Cells were cultured in DMEM (Hyclone, Lot. No. NAA1324) supplemented with 10% FBS in sterile conditions. Cell cultures were maintained in an incubator at  $37^{\circ}\text{C}$ , 5%  $\text{CO}_2$ . Tumor cells were sub-cultured twice a

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week using 0.25% trypsin-EDTA. Cells in log-phase growth were harvested and counted for inoculation.

### 5.1.2 PBMC isolation


60mL of fresh blood was provided by one donator, and PBMCs was isolated as following:

1. Add the same volume of PBS to the blood.
2. Add 10 ml human lymphocyte separation medium to six 50-ml tubes respectively. Carefully layer the 20ml diluted blood over the lymphocyte separation medium using pipette. Do not disturb the surface of the medium.
3. Carefully place the tubes in a desktop centrifuge. Centrifuge at 1500 rpm for 15 min at room temperature. Acceleration 0, no brake.
4. Carefully remove the tubes from the centrifuge and transfer the mononuclear cell layer at the interphase (about 5-12 ml) to a new tube. Fill the tube with sterile PBS making up the volume to 50 ml. Aliquot the fluid and each tube less than 20 ml.
5. Centrifuge at room temperature on a desktop horizontal centrifuge at 1200 rpm for 10 min.
6. Discard the supernatant; wash the cells by adding 20 ml PBS. Centrifuge at 1200 rpm for 10 min.
7. Discard the supernatant. Re-suspend the cells using RPMI1640. Count the cells and dilute the cells to  $4 \times 10^7$ /ml using PRMI1640.
8. Place the cells on ice for later use.

### 5.2 Grouping and dosing

NOD-SCID mice were inoculated with  $4 \times 10^6$  A375-hPDL1(50 $\mu$ L) mixed with  $1 \times 10^6$  of human PBMCs (50 $\mu$ L) subcutaneously under the armpit. The mice were randomized into six groups, 6



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mice each group. Four hours after inoculation, KN035 was administrated to the mice with different doses by i.p. injection. The date was marked by 0 day. The mice were treated Q1W for 4 weeks. When the tumors grown up to 150mm<sup>3</sup>, the tumors were measured twice a week and mice were weighed. Euthanasia the mice using CO<sub>2</sub> after the tumors grown more than 2000mm<sup>3</sup>, dissected the tumors and weighed the tumors. Mice group design is listed in [Table 1](#).

**Table 1      Animal group and drug administration**


Group	Route	Period	Dose (mg/kg)	Volume (mL/kg)	Concentration (mg/mL)
A PBS	IP	Q1W, 4 weeks	0	4	0
B KN035	IP	Q1W, 4 weeks	0.1	4	0.025
C KN035	IP	Q1W, 4 weeks	0.3	4	0.075
D KN035	IP	Q1W, 4 weeks	1	4	0.25
E KN035	IP	Q1W, 4 weeks	3	4	0.75
F KN035	IP	Q1W, 4 weeks	10	4	2.5

### 5.3      Evaluation

Weigh the mice every two weeks, measure the tumor in two dimensions, the length (Y) and the width (X). Calculate the tumor volume and TGI % as the following formulas:

$$V = (X^2Y)/2$$

$$TGI\% = (V_{\text{tumor PBS}} - V_{\text{tumor KN035}}) / (V_{\text{tumor control}}) * 100\%$$

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The tumor volume in PBS group mice was exceeding 2000mm<sup>3</sup> on the 30<sup>th</sup> day. These mice were sacrificed using CO<sub>2</sub> and the tumors were weighed. The mice in other groups were sacrificed on the 34<sup>th</sup> day. Tumors were dissected and weighed.

## 5.4 Inspection

Animal clinical reactions were recorded during the experiment.

## 6 Results

### 6.1 Clinical symptoms

All the mice clinical performances were normal.


### 6.2 Effect on the body weight of KN035 on A375-hPDL1/human PBMC xenografted NOD-SCID mice model

Compared to the PBS group, the body weight of the mice in KN035 0.3mg/kg group significantly decreased on the 9, 13, 23rd day after the first treatment. The body weight of mice in KN035 10mg/kg group significantly decreased on 9 days after the first treatment. ( $P < 0.05$ ,  $P < 0.01$ ). The body weight of the mice in other groups did not show significant differences compared with those in PBS group. ( $P \geq 0.05$ ). ([Table 2](#), [Figure 1](#))

### 6.3 Effect on the tumor growth of KN035 on A375-hPDL1/human PBMC xenografted NOD-SCID mice model

Tumor volume of the mice in the groups of KN035 0.1mg/kg, 0.3mg/kg, 1mg/kg, 10mg/kg treatment were significantly decreased on the days of 9, 13, 16, 20, 23, 27, 30<sup>th</sup> day after the first dose of treatment, the tumor volume of mice in the group of KN035 3mg/kg were decreased on the days of 9, 13, 16, 20, 23, 27<sup>th</sup> days after the first treatment compared to PBS treated group ( $P < 0.05$ ,  $P < 0.01$ ). ([Table 3](#), [Figure 2](#), [Figure 3](#))

Compared to the PBS treated group, the tumor growth inhibition rate (TGI %) in groups of 0.1mg/kg, 0.3mg/kg, 1mg/kg, 3mg/kg, 10mg/kg treatment were 56.6%, 77.09%, 77.04%, 46.49%, 68.57% respectively ([Table 4](#)).

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## 6.4 Effect on the tumors weight of KN035on A375-hPDL1/human PBMC xenograftedNOD-SCID mice model

The tumors weight of KN035 0.1mg/kg, 0.3mg/kg, 1mg/kg, 10mg/kg treatment groups were  $1.06 \pm 0.16$ g,  $0.8 \pm 0.13$ g,  $0.93 \pm 0.23$ g,  $1.01 \pm 0.26$ g respectively on the 34<sup>th</sup> day, which were significantly decreased compared to the PBS treated group(tumor weight  $1.66 \pm 0.11$ g on the 30<sup>th</sup> day). ( $P < 0.05$ ,  $P < 0.01$ ) (Figure 4)

## 7 Conclusion

In this study, we established a mouse model by subcutaneously inoculation of mixed  $4 \times 10^6$  A375-hPDL1 (50 $\mu$ L) and  $1 \times 10^6$  human PBMCs (50 $\mu$ L) on NOD-SCID mice. Four hours later, the mice received KN035 by i.p. injection with different doses (0.1, 0.3, 1, 3, 10mg/kg, Q1W for four weeks). The results showed that on the A375-hPDL1/human PBMC-NOD/SCID xenograft model KN035 had significant antitumor effect on the doses of 0.1mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg and 10 mg/kg. And it did not show an obvious dose-dependence effect.



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## 8 Tables

**Table 2 Effect on the body weight of KN035 on A375-hPDL1/human PBMC xenografted NOD-SCID mice model (g, Mean±SEM)**

Day	Group					
	A PBS	B KN035 0.1mg/kg	C KN035 0.3mg/kg	D KN035 1mg/kg	E KN035 3mg/kg	F KN035 10 mg/kg
9	22.61±0.33	22.4±0.98	20.85±0.57*	21.8±0.16	21.15±0.71	21.31±0.35*
13	22.93±0.34	22.13±0.81	21.35±0.44*	22.12±0.32	21.73±0.74	22±0.46
16	23.08±0.25	22.95±0.8	22.02±0.45	23.1±0.32	22.14±0.89	22.72±0.37
20	24.07±0.38	23.85±0.81	22.72±0.45	23.13±0.32	22.77±0.66	23.21±0.39
23	23.7±0.32	22.98±0.88	22±0.38*	22.77±0.42	22.23±0.59	22.78±0.29
27	23.4±0.54	23.53±0.93	22±0.55	23.08±0.36	22.7±0.66	23.28±0.4
30	23.52±0.44	23.82±1.01	22.45±0.41	23.1±0.38	22.78±0.84	23.75±0.64
34	-	23.45±1.03	22.48±0.35	22.03±0.86	22.27±1.26	22.41±0.75

-: Mice in group A were sacrificed because of tumor volume exceeded 2000mm<sup>3</sup>, no data available on the 34<sup>th</sup> day; T test vs PBS, \*P<0.05



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**Table 3 Effect on the tumor volume of KN035 on A375-hPDL1/human PBMC xenografted NOD-SCID mice model (mm<sup>3</sup>, Mean±SEM)**

Day	Group					
	A PBS	B KN035 0.1mg/kg	C KN035 0.3mg/kg	D KN035 1mg/kg	E KN035 3mg/kg	F KN035 10 mg/kg
9	50.9±8.56	26.68±4.25*	3.14±3.14**	14.78±5.24**	20.35±5.38*	9.76±6.46**
13	77.55±15.31	19.37±9.74*	7.53±3.55**	17.37±5.81**	33.74±9.3*	13.51±9.39**
16	115.27±23.5	42.1±12.41*	16.67±4.41**	17.07±6.18**	45.32±13.92*	25.79±12.39**
20	384.69±77.98	76.46±20.19**	35.57±8.21**	40.31±17.04**	144.16±66.23*	69.35±31.65**
23	622.29±97.58	170.88±57.09**	73.51±21.43**	78.01±27.65**	185.51±60.02**	134.32±61.13**
27	1166.75±182.27	462.15±125.12**	243.13±55.04**	250.93±77.31**	373.11±119.09**	348.39±113.87**
30	1723.64±257.27	748.07±164.39**	394.94±66.79**	395.76±124.2**	922.25±371.85	541.81±147.28**
34	-	749.13±200.35	489.83±86.82	534.38±166.13	707.64±168	768.8±248.19

-: Mice in group A were sacrificed because of tumor volume exceeded 2000mm<sup>3</sup>, no data available on the 34<sup>th</sup> day; T test vs PBS, \*P<0.05, \*\*P<0.0,1



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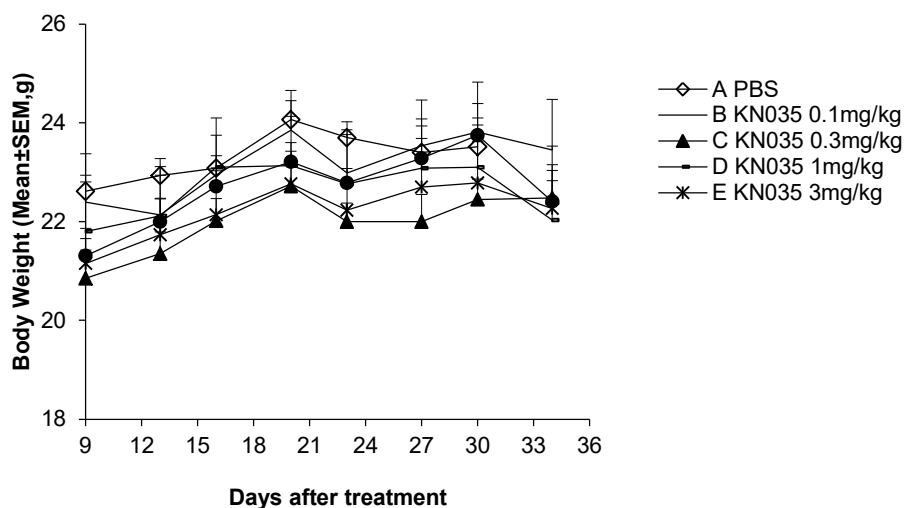
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**Table 4 Effect on the tumor inhibition rate of KN035 on A375-hPDL1/human PBMC xenografted NOD-SCID mice model TGI(%)**

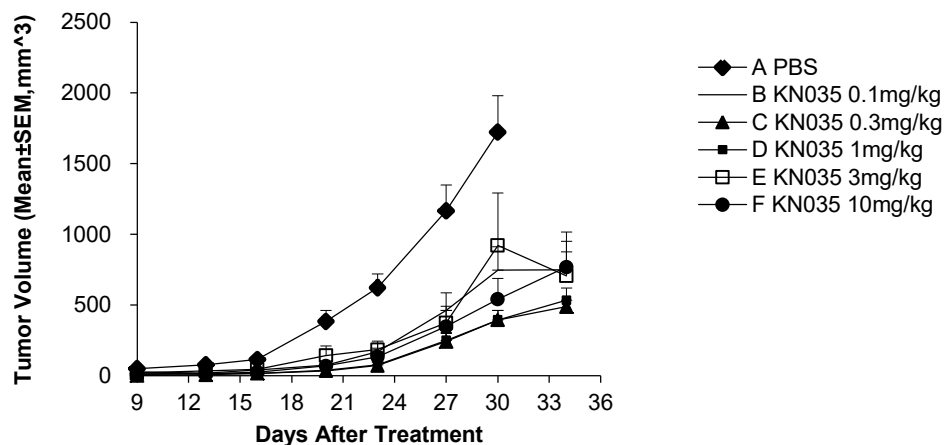
Day	Group				
	B KN035 0.1mg/kg	C KN035 0.3mg/kg	D KN035 1mg/kg	E KN035 3mg/kg	F KN035 10mg/kg
9	47.58	93.84	70.95	60.02	80.81
13	75.02	90.30	77.61	56.49	82.58
16	63.47	85.54	85.19	60.68	77.62
20	80.12	90.75	89.52	62.53	81.97
23	72.54	88.19	87.46	70.19	78.42
27	60.39	79.16	78.49	68.02	70.14
30	56.60	77.09	77.04	46.49	68.57

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## 9 Figures

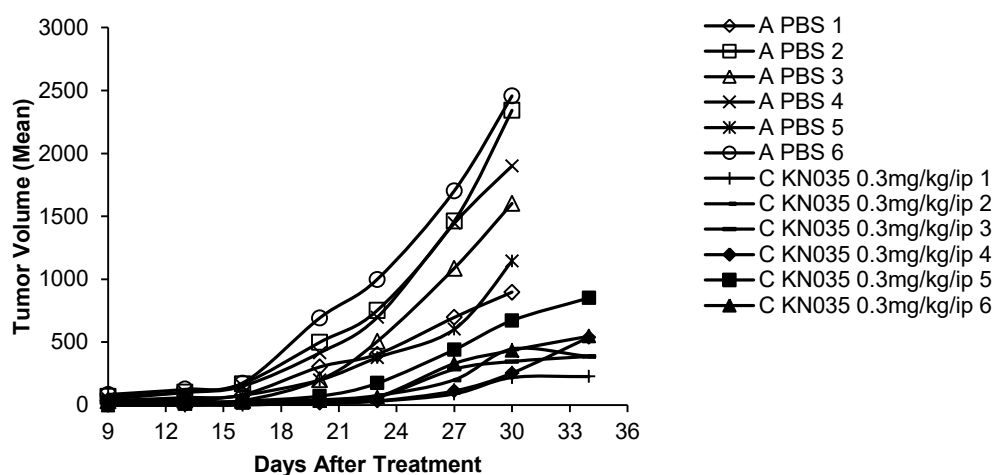


**Figure 1** Effect on the body weight of KN035 on A375-hPDL1/human PBMC xenografted model




**Figure 2** Effect on the tumor volume of KN035 on A375-hPDL1/human PBMC xenografted model

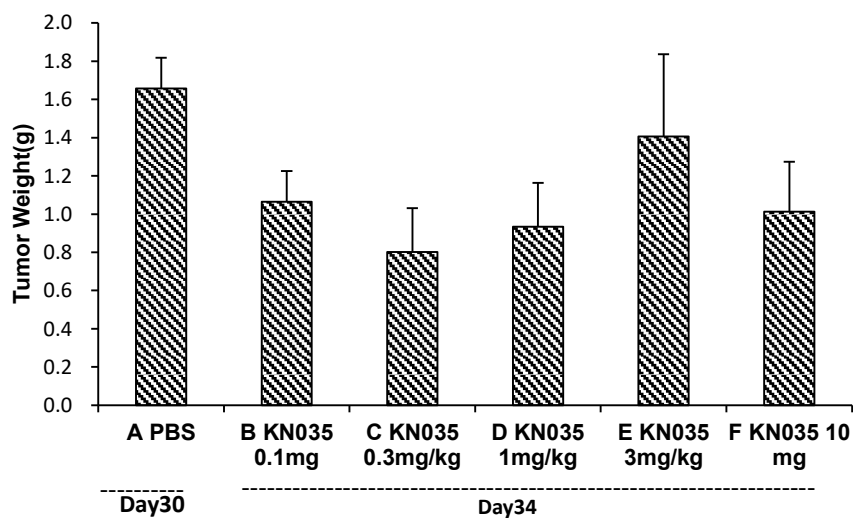
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**Figure 3** Tumor growth curves of mice in groups of PBS and KN035 0.3mg/kg treatment group on A375-hPDL1/PBMC xenograft tumor model



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**Figure 4** Effect on the tumor weight of KN035 on A375-hPDL1/human PBMC xenografted model

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## 10 Appendix

### Appendix 1 Body weight of mice in this study (g)

Group	Animal #	Days Post Treatment							
		9	13	16	20	23	27	30	34
A PBS	1	22.9	22.9	23.7	25.2	24.9	25.3	24.7	-
	2	23.6	23.3	23.3	24.4	23.9	23.6	24.5	-
	3	21.4	21.8	22.0	22.4	22.6	22.2	22.5	-
	4	21.9	22.1	22.7	23.8	23.3	23.3	23.3	-
	5	22.9	23.7	23.4	24.3	23.4	21.7	22.1	-
	6	23.0	23.8	23.4	24.3	24.1	24.3	24.0	-
	Mean	22.61	22.93	23.08	24.07	23.70	23.40	23.52	-
	SD	0.80	0.83	0.62	0.93	0.79	1.33	1.07	-
	SEM	0.33	0.34	0.25	0.38	0.32	0.54	0.44	-
B KN035 0.1mg/kg	1	25.5	24.8	25.3	26.0	26.1	26.5	27.3	27.0
	2	20.0	20.0	20.9	22.9	21.3	21.6	23.1	21.8
	3	20.7	21.2	22.0	22.7	21.8	22.2	22.2	22.6
	4	21.3	21.5	22.3	22.8	22.3	22.6	22.0	22.8
	5	21.7	20.9	21.7	22.0	21.1	21.9	21.7	20.5
	6	25.3	24.4	25.5	26.7	25.3	26.4	26.6	26.0
	Mean	22.40	22.13	22.95	23.85	22.98	23.53	23.82	23.45
	SD	2.39	1.98	1.96	1.97	2.16	2.28	2.48	2.52
	SEM	0.98	0.81	0.80	0.81	0.88	0.93	1.01	1.03
C KN035 0.3mg/kg	1	21.5	22.2	22.6	23.5	21.8	23.5	23.1	23.2
	2	21.9	21.9	22.5	23.7	22.9	22.9	23.4	21.8
	3	22.5	22.5	23.4	22.1	23.4	23.2	23.4	23.7
	4	19.1	19.9	20.3	21.4	21.2	20.6	21.1	21.4
	5	19.3	20.2	21.2	21.7	21.2	21.3	22.2	22.4
	6	21.0	21.4	22.1	23.9	21.5	20.5	21.5	22.4
	Mean	20.85	21.35	22.02	22.72	22.00	22.00	22.45	22.48
	SD	1.39	1.07	1.11	1.11	0.93	1.36	1.00	0.85
	SEM	0.57	0.44	0.45	0.45	0.38	0.55	0.41	0.35
D KN035 1mg/kg	1	21.2	21.9	22.9	23.0	22.6	22.3	23.2	23.3
	2	22.3	22.7	23.0	23.7	23.2	23.8	22.3	21.9

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	3	21.9	22.1	23.7	23.5	23.2	23.3	23.9	22.1
	4	21.5	21.5	22.3	22.1	21.9	22.3	22.8	23.8
	5	21.9	23.3	24.4	24.1	24.3	24.4	24.4	23.1
	6	22.0	21.2	22.4	22.4	21.4	22.4	22.0	18.0
	<b>Mean</b>	<b>21.80</b>	<b>22.12</b>	<b>23.10</b>	<b>23.13</b>	<b>22.77</b>	<b>23.08</b>	<b>23.10</b>	<b>22.03</b>
	<b>SD</b>	<b>0.39</b>	<b>0.78</b>	<b>0.78</b>	<b>0.78</b>	<b>1.04</b>	<b>0.89</b>	<b>0.93</b>	<b>2.10</b>
	<b>SEM</b>	<b>0.16</b>	<b>0.32</b>	<b>0.32</b>	<b>0.32</b>	<b>0.42</b>	<b>0.36</b>	<b>0.38</b>	<b>0.86</b>
<b>E KN035 3mg/kg</b>	1	21.5	21.8	23.3	23.0	22.4	23.0	23.3	23.3
	2	18.1	18.6	18.0	19.8	19.4	20.8	21.8	21.4
	3	23.3	24.2	24.2	24.7	23.5	24.7	24.9	24.7
	4	21.6	22.2	22.1	23.5	23.0	23.2	23.2	22.3
	5	20.5	21.4	21.9	22.8	22.7	23.8	24.3	25.2
	6	22.0	22.2	23.4	22.8	22.4	20.7	19.2	16.7
	<b>Mean</b>	<b>21.15</b>	<b>21.73</b>	<b>22.14</b>	<b>22.77</b>	<b>22.23</b>	<b>22.70</b>	<b>22.78</b>	<b>22.27</b>
	<b>SD</b>	<b>1.74</b>	<b>1.81</b>	<b>2.19</b>	<b>1.62</b>	<b>1.45</b>	<b>1.62</b>	<b>2.05</b>	<b>3.08</b>
	<b>SEM</b>	<b>0.71</b>	<b>0.74</b>	<b>0.89</b>	<b>0.66</b>	<b>0.59</b>	<b>0.66</b>	<b>0.84</b>	<b>1.26</b>
<b>F KN035 10mg/kg</b>	1	20.6	20.7	22.0	22.4	22.1	23.2	24.0	23.8
	2	20.8	21.2	21.9	22.0	22.0	21.7	20.9	19.9
	3	20.3	21.3	22.1	23.1	22.4	22.8	23.3	23.2
	4	22.0	22.2	22.8	23.3	23.4	24.1	25.4	22.2
	5	22.5	23.6	24.2	24.6	23.7	24.4	24.6	24.6
	6	21.6	23.0	23.3	23.9	23.1	23.5	24.3	20.7
	<b>Mean</b>	<b>21.31</b>	<b>22.00</b>	<b>22.72</b>	<b>23.21</b>	<b>22.78</b>	<b>23.28</b>	<b>23.75</b>	<b>22.41</b>
	<b>SD</b>	<b>0.86</b>	<b>1.13</b>	<b>0.91</b>	<b>0.95</b>	<b>0.71</b>	<b>0.97</b>	<b>1.56</b>	<b>1.83</b>
	<b>SEM</b>	<b>0.35</b>	<b>0.46</b>	<b>0.37</b>	<b>0.39</b>	<b>0.29</b>	<b>0.40</b>	<b>0.64</b>	<b>0.75</b>



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## Appendix 2 Tumor volume (mm<sup>3</sup>)

Group	Animal #	Days Post Treatment							
		9	13	16	20	23	27	30	34
A PBS	1	35.46	58.88	80.92	303.52	403.48	697.77	896.68	-
	2	68.99	103.22	170.16	498.63	751.83	1463.11	2341.26	-
	3	33.72	38.03	36.87	200.70	505.53	1087.39	1602.28	-
	4	49.03	100.76	150.59	414.91	697.42	1445.55	1900.55	-
	5	34.58	38.15	77.91	199.46	376.98	603.54	1143.85	-
	6	83.60	126.27	175.14	690.93	998.51	1703.13	2457.20	-
	Mean	50.90	77.55	115.27	384.69	622.29	1166.75	1723.64	-
	SD	20.97	37.51	57.56	191.01	239.02	446.48	630.18	-
	SEM	8.56	15.31	23.50	77.98	97.58	182.27	257.27	-
B KN035 0.1mg/kg	1	22.75	0.00	27.26	55.09	130.27	575.01	1004.59	1026.61
	2	19.61	11.46	14.41	17.80	38.84	43.64	129.91	136.61
	3	26.82	0.00	67.95	133.42	169.02	474.29	908.94	478.02
	4	17.92	16.13	19.52	54.71	110.15	396.39	644.02	754.12
	5	26.34	24.58	32.71	56.36	134.65	315.64	526.54	550.82
	6	46.65	64.06	90.76	141.37	442.35	967.96	1274.40	1548.63



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	<b>Mean</b>	<b>26.68</b>	<b>19.37</b>	<b>42.10</b>	<b>76.46</b>	<b>170.88</b>	<b>462.15</b>	<b>748.07</b>	<b>749.13</b>
	<b>SD</b>	<b>10.41</b>	<b>23.87</b>	<b>30.40</b>	<b>49.46</b>	<b>139.84</b>	<b>306.49</b>	<b>402.67</b>	<b>490.76</b>
	<b>SEM</b>	<b>4.25</b>	<b>9.74</b>	<b>12.41</b>	<b>20.19</b>	<b>57.09</b>	<b>125.12</b>	<b>164.39</b>	<b>200.35</b>
<b>C KN035 0.3mg/kg</b>	1	0.00	0.00	0.00	22.11	31.90	88.96	219.14	227.82
	2	0.00	20.08	24.16	41.66	75.90	200.21	444.20	386.68
	3	0.00	0.00	9.58	29.38	61.58	285.33	346.03	386.68
	4	0.00	0.00	16.02	14.06	32.81	113.38	254.01	538.56
	5	18.82	12.82	30.35	71.63	174.31	440.87	671.90	850.99
	6	0.00	12.25	19.91	34.61	64.57	330.03	434.37	548.24
	<b>Mean</b>	<b>3.14</b>	<b>7.53</b>	<b>16.67</b>	<b>35.57</b>	<b>73.51</b>	<b>243.13</b>	<b>394.94</b>	<b>489.83</b>
	<b>SD</b>	<b>7.68</b>	<b>8.69</b>	<b>10.79</b>	<b>20.10</b>	<b>52.49</b>	<b>134.82</b>	<b>163.61</b>	<b>212.67</b>
	<b>SEM</b>	<b>3.14</b>	<b>3.55</b>	<b>4.41</b>	<b>8.21</b>	<b>21.43</b>	<b>55.04</b>	<b>66.79</b>	<b>86.82</b>
<b>D KN035 1mg/kg</b>	1	28.70	32.56	30.23	91.28	166.44	494.50	811.35	1121.37
	2	11.34	0.00	0.00	0.00	12.84	59.52	121.12	177.95
	3	24.10	25.17	35.12	90.50	155.87	451.65	705.53	956.15
	4	24.56	28.17	24.00	38.04	57.70	237.19	263.14	336.02
	5	0.00	0.00	0.00	0.00	13.91	46.83	77.90	173.07
	6	0.00	18.29	13.09	22.01	61.31	215.88	395.56	441.74
	<b>Mean</b>	<b>14.78</b>	<b>17.37</b>	<b>17.07</b>	<b>40.31</b>	<b>78.01</b>	<b>250.93</b>	<b>395.76</b>	<b>534.38</b>



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	<b>SD</b>	<b>12.85</b>	<b>14.23</b>	<b>15.14</b>	<b>41.73</b>	<b>67.72</b>	<b>189.38</b>	<b>304.21</b>	<b>406.93</b>
	<b>SEM</b>	<b>5.24</b>	<b>5.81</b>	<b>6.18</b>	<b>17.04</b>	<b>27.65</b>	<b>77.31</b>	<b>124.20</b>	<b>166.13</b>
<b>E KN035 3mg/kg</b>	1	41.14	68.17	87.64	247.71	403.54	839.10	1197.53	1271.98
	2	23.01	27.94	50.29	74.62	159.10	434.11	686.41	1077.96
	3	20.95	25.41	17.98	29.11	54.99	95.44	331.84	288.68
	4	16.38	15.92	9.86	34.77	60.64	102.47	216.90	250.66
	5	20.60	54.73	83.69	430.06	329.60	548.12	2641.60	728.34
	6	0.00	10.29	22.47	48.72	105.16	219.42	459.22	628.24
	<b>Mean</b>	<b>20.35</b>	<b>33.74</b>	<b>45.32</b>	<b>144.16</b>	<b>185.51</b>	<b>373.11</b>	<b>922.25</b>	<b>707.64</b>
	<b>SD</b>	<b>13.19</b>	<b>22.79</b>	<b>34.10</b>	<b>162.24</b>	<b>147.02</b>	<b>291.71</b>	<b>910.83</b>	<b>411.51</b>
	<b>SEM</b>	<b>5.38</b>	<b>9.30</b>	<b>13.92</b>	<b>66.23</b>	<b>60.02</b>	<b>119.09</b>	<b>371.85</b>	<b>168.00</b>
<b>F KN035 10mg/kg</b>	1	0.00	0.00	11.62	36.21	57.72	267.27	478.64	663.82
	2	0.00	0.00	0.00	21.97	25.28	141.93	189.52	209.14
	3	36.62	55.63	79.61	213.19	411.00	809.02	1105.31	1685.19
	4	21.97	25.44	39.01	96.77	195.27	533.68	779.70	1230.29
	5	0.00	0.00	0.00	0.00	22.68	48.67	156.49	83.13
	6	0.00	0.00	24.51	47.98	93.98	289.78	541.22	741.26
	<b>Mean</b>	<b>9.76</b>	<b>13.51</b>	<b>25.79</b>	<b>69.35</b>	<b>134.32</b>	<b>348.39</b>	<b>541.81</b>	<b>768.80</b>
	<b>SD</b>	<b>15.82</b>	<b>23.01</b>	<b>30.35</b>	<b>77.52</b>	<b>149.74</b>	<b>278.92</b>	<b>360.75</b>	<b>607.93</b>

<div><b>ALPHAMAB</b></div> <div>R&amp;D Report</div>	
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	SEM	6.46	9.39	12.39	31.65	61.13	113.87	147.28	248.19
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