Safety and tolerability of Miltuximab® - a first in human study in patients with advanced solid cancers

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Supplementary Files

Supplementary Table 1a. Normal organ absorbed doses (mSv/MBq) across all patients

	Normal organ absorbed dose (mSv/MBq)				
Organ	Mean	Median	SD	Min	Max
Adrenals	0.11	0.10	0.01	0.10	0.13
Brain	0.03	0.03	0.01	0.02	0.04
Gallbladder Wall	0.16	0.16	0.01	0.14	0.18
LLI Wall	0.04	0.04	0.01	0.03	0.06
Small Intestine	0.06	0.06	0.01	0.05	0.07
Stomach Wall	0.07	0.06	0.01	0.06	0.08
ULI Wall	0.07	0.07	0.01	0.06	0.08
Heart Wall	0.15	0.15	0.03	0.11	0.19
Kidneys	0.08	0.08	0.01	0.07	0.10
Liver	0.62	0.65	0.07	0.48	0.69
Lungs	0.11	0.12	0.01	0.10	0.13
Muscle	0.05	0.05	0.01	0.04	0.06
Pancreas	0.11	0.10	0.01	0.09	0.13
Red Marrow	0.09	0.09	0.02	0.06	0.13
Osteogenic Cells	0.16	0.16	0.02	0.12	0.20
Skin	0.03	0.03	0.00	0.03	0.04
Spleen	0.31	0.27	0.11	0.20	0.53
Testes	0.03	0.03	0.01	0.02	0.04
Thymus	0.05	0.05	0.01	0.05	0.07
Thyroid	0.04	0.04	0.01	0.03	0.05
Bladder Wall	0.04	0.04	0.01	0.03	0.06
Residual Total Body	0.06	0.06	0.01	0.06	0.08
WB ED	0.09	0.09	0.01	0.08	0.10

Supplementary Table 1b. Normal organ absorbed doses (mSv/MBq) for individual patients

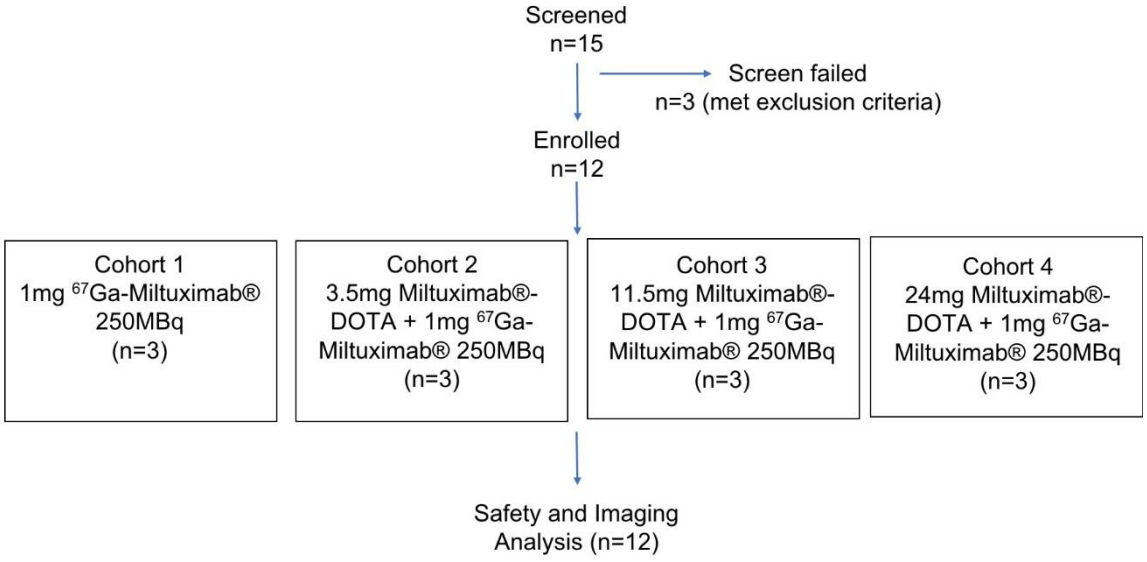
	Normal organ absorbed dose (mSv/MBq)											
Organ	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12
Adrenals	0.13	0.10	0.10	0.11	0.10	0.10	0.11	0.10	0.11	0.10	0.10	0.10
Brain	0.04	0.03	0.03	0.03	0.02	0.03	0.03	0.03	0.03	0.03	0.03	0.04
Gallbladder Wall	0.18	0.16	0.16	0.17	0.16	0.14	0.17	0.16	0.17	0.14	0.15	0.14
LLI Wall	0.06	0.04	0.04	0.04	0.03	0.04	0.04	0.04	0.04	0.05	0.05	0.05
Small Intestine	0.07	0.05	0.06	0.06	0.05	0.05	0.06	0.06	0.06	0.06	0.06	0.07
Stomach Wall	0.08	0.06	0.06	0.06	0.06	0.06	0.07	0.06	0.07	0.06	0.07	0.07
ULI Wall	0.08	0.06	0.06	0.07	0.06	0.06	0.07	0.07	0.07	0.07	0.07	0.07
Heart Wall	0.17	0.15	0.11	0.14	0.15	0.15	0.12	0.18	0.16	0.19	0.14	0.11
Kidneys	0.10	0.08	0.08	0.08	0.08	0.07	0.09	0.08	0.09	0.08	0.08	0.08
Liver	0.69	0.65	0.64	0.69	0.68	0.56	0.66	0.60	0.68	0.51	0.56	0.48
Lungs	0.12	0.11	0.10	0.12	0.10	0.12	0.11	0.12	0.13	0.12	0.11	0.11
Muscle	0.06	0.04	0.04	0.04	0.04	0.04	0.05	0.05	0.05	0.05	0.05	0.05
Pancreas	0.13	0.10	0.10	0.10	0.10	0.09	0.12	0.10	0.11	0.10	0.11	0.11
Red Marrow	0.08	0.11	0.09	0.13	0.07	0.11	0.10	0.08	0.09	0.09	0.06	0.11
Osteogenic Cells	0.20	0.15	0.15	0.16	0.12	0.15	0.16	0.16	0.16	0.17	0.17	0.20
Skin	0.04	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Spleen	0.36	0.27	0.24	0.22	0.31	0.20	0.53	0.21	0.27	0.22	0.37	0.49
Testes	0.04	0.03	0.03	0.03	0.02	0.03	0.03	0.03	0.03	0.04	0.04	0.04
Thymus	0.07	0.05	0.05	0.05	0.05	0.05	0.05	0.06	0.05	0.06	0.06	0.05
Thyroid	0.05	0.03	0.03	0.03	0.03	0.03	0.04	0.04	0.04	0.04	0.04	0.04
Bladder Wall	0.06	0.03	0.04	0.04	0.03	0.04	0.04	0.04	0.04	0.05	0.05	0.05
Residual Total Body	0.08	0.06	0.06	0.06	0.06	0.06	0.07	0.06	0.07	0.06	0.06	0.07
WB ED	0.10	0.09	0.09	0.10	0.08	0.09	0.10	0.09	0.10	0.09	0.09	0.10

Supplementary Table 2. Statistical analyses of differences in percentage injected dose ^{67}Ga-Miltuximab® over time and at individual time points. Figure 3 describes uptake over 4 cohorts of patients receiving varying levels of unlabeled Miltuximab® (Cohort 1: 0 mg; Cohort 2: 3.5 mg; Cohort 3: 11.5 mg; Cohort 4: 24 mg). Full statistical analyses of these data are shown here. The differences across all time course was investigated using mixed-effects model for repeated measures approach. Further assessment for the differences in uptake across time course between each pair of cohorts was performed using Tukey's honest significance test. The difference analysis in the uptake among the Cohorts was reported as p values, significant values are bolded. To test the differences in uptake between cohorts at individual time points, we used ANOVA test with Bonferroni correction. For time point analysis, differences were reported as p values, any p values that did not reach significance ($p<0.05$) were not reported (blank). Significant values are bolded

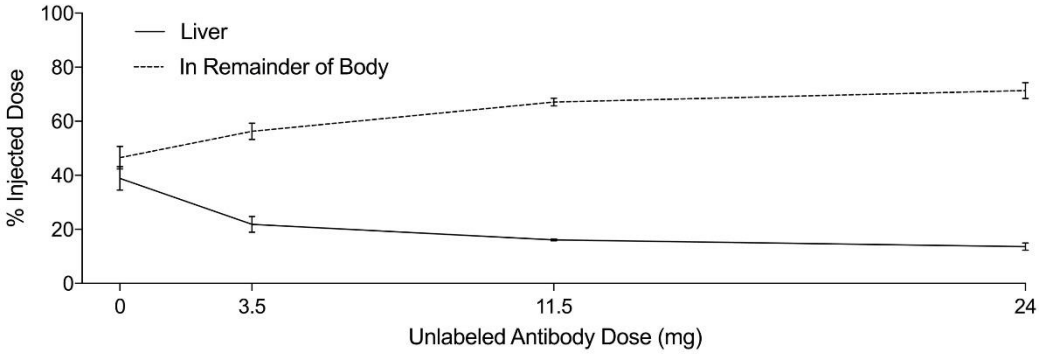
Data set	Test Comparison	Difference Analysis (p value)						
		Across All Time Course	At Individual Time Points					
			0.5	6	24	48	72	144
Liver	Cohort 1 v Cohort 2	0.309	0.013					
	Cohort 2 v Cohort 3	0.627						
	Cohort 3 v Cohort 4	0.102				0.009		
	Cohort 1 v Cohort 3	0.036	0.002	0.022				
	Cohort 1 v Cohort 4	0.002	0.001	0.002	0.006	0.007		
	Cohort 2 v Cohort 4	0.019		0.011	0.007	0.018		
	Difference in Cohorts	0.002	0.004	0.006	0.018	0.018		
In whole body	Cohort 1 v Cohort 2	0.787						
	Cohort 2 v Cohort 3	0.990						
	Cohort 3 v Cohort 4	1.00						
	Cohort 1 v Cohort 3	0.919						
	Cohort 1 v Cohort 4	0.906						
	Cohort 2 v Cohort 4	0.993						
	Difference in Cohorts	0.815						
In remainder of body	Cohort 1 v Cohort 2	0.805						
	Cohort 2 v Cohort 3	0.304						
	Cohort 3 v Cohort 4	0.407						
	Cohort 1 v Cohort 3	0.757	0.008					
	Cohort 1 v Cohort 4	0.110	0.002					
	Cohort 2 v Cohort 4	0.031	0.046					
	Difference in Cohorts	0.039	0.012					

Supplementary Table 3. Pharmacokinetic analysis using ELISA and gamma count data. Table 3 shows individual patient Miltuximab® concentration in ng/ml for patients 7, 8, 9, 10 and 12 together with the max Gamma count reading (counts per minute, cpm) taken 1 h post infusion. Area under the curve was calculated for each patient and per cohort. Blood Clearance Rate half lives ($BCR_{1/2}$) were calculated by fitting on data of individual patients within each cohort, using one-phase decay methods. Cohort averages are shown with 95% confidence intervals. P values are shown for differences in AUC and $BCR_{1/2}$.

Patient	C_{max} (ng/mL)	AUC (95% CI)	BCR half life (h) (95% CI)	$Gamma_{max}$ (cpm)	AUC (95% CI)	BCR half life (h) (95% CI)
Patient 7	668	5,790	5.7 (4.8 - 6.8)	4,764,767	4,821,474	4.6 (4.0 - 5.3)
Patient 8	1,180	30,119	5.1 (3.8 - 7)	5,153,898	8,040,522	9.6 (7.6 - 12.1)
Patient 9	1,288	10,680	4.4 (3.8 - 5.1)	5,759,997	8,264,123	7.8 (7.0 - 8.8)
Patient 10	2,383	51,864	15.6 (11.5 - 21.3)	5,534,414	9,384,462	8.9 (6.2 - 12.9)
Patient 11		Not available		3,076,467	6,170,099	12.3 (11.5 - 13.2)
Patient 12	2,881	80,356	20.1 (15.7 - 25.6)	4,488,965	10,123,252	15.8 (9.8 - 25.5)
Cohort 3	1,045	66,110 (46,724-85,496)	5 (3.7 - 6.6)	5,226,220	7,042,039 (5,588,438-8,495,641)	7.3 (6.3 - 8.4)
Cohort 4	2,632	15,529 (3,911-27,148)	18.2 (13.4 - 24.6)	4,366,615	8,559,271 (6,773,468-10,345,073)	12 (8.7 - 16.3)
Cohort 4 - Cohort 3		50,580 (29,491-68,169)				1,517,231 (503,342-3, 411,892)
P value (Cohort 4 vs 3)		<0.0001	<0.0001		0.094	0.361

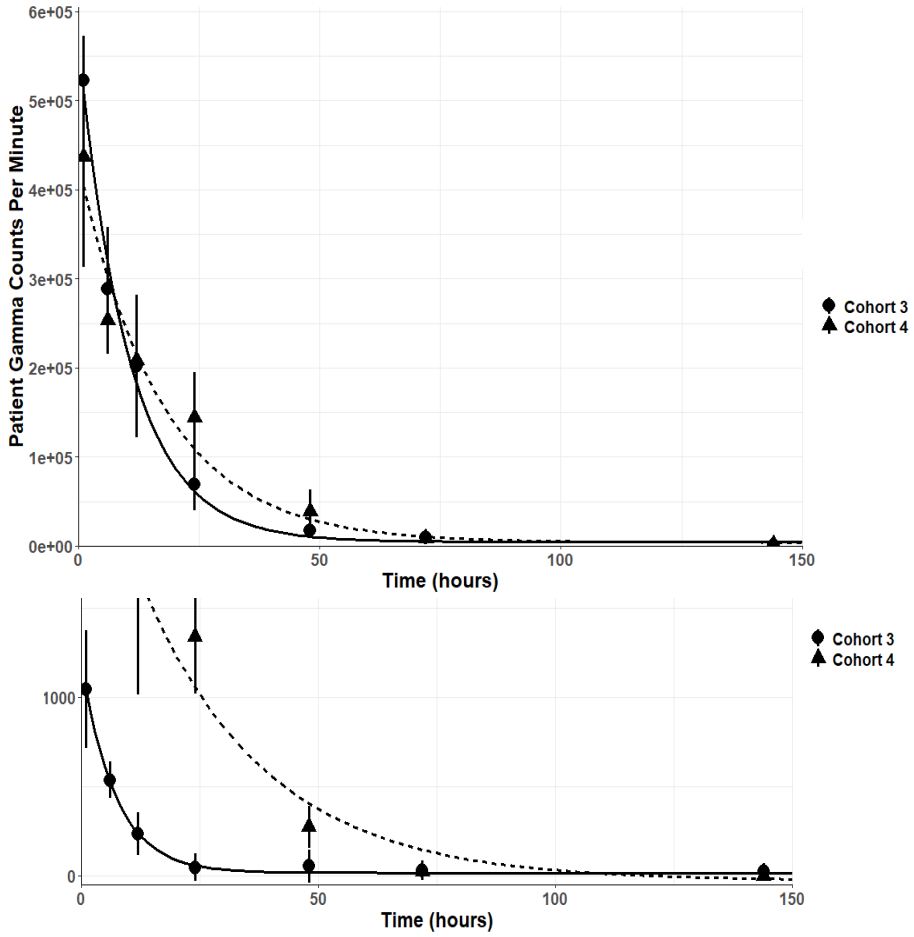


Supplementary Figure 1. CONSORT diagram



Supplementary Figure 2. Cold dosing effect on mean percentage Injected Dose in liver and remainder of body at 30 min post [^{67}Ga]Ga-DOTA-Miltuximab® infusion. The increase in % Injected Dose recorded in Remainder of Body, as compared to Liver, was highly correlated with the cold dose (Pearson's correlation r = 0.88, p<0.001). Linear regression analysis was used to investigate the association between the increase (in percentage) in % Injected Dose recorded in Remainder of Body as compared to the % Injected Dose in the Liver, and the amount of unlabelled Miltuximab® dose (0, 3.5, 11.5 and 24 mg; i.e. Cohort 1, Cohort 2, Cohort 3, and Cohort 4, respectively). Using Cohort 1 as reference, Cohort 2 associated with ~1.44-fold increase (p = 0.067), Cohort 3 associated with ~2.91-fold increase (p = 0.003), and Cohort 4 associated with ~4.14-fold increase (p<0.001) in % Injected Dose recorded in Remainder of Body as compared to Liver

B



Supplementary Figure 3. The values of cohort 3 and 4 were calculated as the average of each patient in the cohort. Error bars were presented as cohorts values +/- 1 SD. The curves were fitted on data of individual patients within each cohort, using one-phase decay methods. A. [^{67}Ga]Ga-DOTA-Miltuximab® blood clearance for all patients in Cohorts 3 and 4 as measured by radioactivity. B. Miltuximab® blood clearance rate for Cohort 3 (Patient 7, 8, 9) and Cohort 4 (Patient 10, 12) as measured by ELISA