

Figure 1**SEQ ID No. 7 (KRAS4A)**

10	20	30	40	50
MTEYKLVVVG	<u>A</u> GGVGKSALT	IQLIQNHFVD	EYDPTIEDSY	RKQVVIDGET
60	70	80	90	100
CLLDILDTAG	<u>Q</u> EEYSAMRDQ	YMRTGEGFLC	VFAINNNTKSF	EDIHHYREQI
110	120	130	140	150
KRVKDSSEDP	MVLVGKNCDL	PSRTVDTKQA	QDLARSYGIP	FIETSA <u>A</u> KTRQ
160	170	180		
RVE <u>D</u> AFYTLV	REIRQYRLKK	ISKEEKTGPG	VKIKKCIIM	

SEQ ID No. 8 (HRAS4A)

10	20	30	40	50
MTEYKLVVVG	<u>A</u> GGVGKSALT	IQLIQNHFVD	EYDPTIEDSY	RKQVVIDGET
60	70	80	90	100
CLLDILDTAG	<u>Q</u> EEYSAMRDQ	YMRTGEGFLC	VFAINNNTKSF	EDIHQYREQI
110	120	130	140	150
KRVKDSDDVP	MVLVGKNCDL	AARTVESRQA	QDLARSYGIP	YIETSAKTRQ
160	170	180		
GVEDAFYTLV	REIRQHKLRK	LNPPDESGPG	CMSCKCVLS	

SEQ ID No. 9 (NRAS)

10	20	30	40	50
MTEYKLVVVG	<u>A</u> GGVGKSALT	IQLIQNHFVD	EYDPTIEDSY	RKQVVIDGET
60	70	80	90	100
CLLDILDTAG	<u>Q</u> EEYSAMRDQ	YMRTGEGFLC	VFAINNNTKSF	ADINLYREQI
110	120	130	140	150
KRVKDSDDVP	MVLVGKNCDL	PTRTVDTKQA	HELAksYGIP	FIETSAKTRQ
160	170	180		
GVEDAFYTLV	REIRQYRMKK	LNSSDDGTQG	CMGLPCVVM	

SEQ ID No. 24 (KRAS4B)

10	20	30	40	50
MTEYKLVVVG	<u>A</u> GGVGKSALT	IQLIQNHFVD	EYDPTIEDSY	RKQVVIDGET
60	70	80	90	100
CLLDILDTAG	<u>Q</u> EEYSAMRDQ	YMRTGEGFLC	VFAINNNTKSF	EDIHHYREQI
110	120	130	140	150
KRVKDSSEDP	MVLVGKNCDL	PSRTVDTKQA	QDLARSYGIP	FIETSA <u>A</u> KTRQ
160	170	180		
GVD <u>D</u> AFYTLV	REIRKHKEKM	SKDGKKKKKK	SKTKCVIM	

Figure 1 (continued)**SEQ ID No. 25 (HRASIDX)**

10	20	30	40	50
MTEYKLVVVG	AGGVGKSALT	IQLIQNHFVD	EYDPTIEDSY	RKQVVIDGET
60	70	80	90	100
CLLDILDTAG	QEEYSAMRDQ	YMRTGEGFLC	VFAINNTKSF	EDIHQYREQI
110	120	130	140	150
KRVKDSDDVP	MVLVGNKCDL	AARTVESRQA	QDLARSYGIP	YIETSAKTRQ
160	170	180		
GSRSGSSSSS	GTLWDPPGPM			

Figure 2

Parameters	Abraxane Phase III		Nimotuzumab Original Analysis Phase IIIA*		Nimotuzumab IPCW Analysis (Phase IIIA)**		Nimotuzumab Extended Cox Model Analysis (Phase IIIA) updated data set *** / 2nd analysis original data set	
	All study Population	Subpopulation KRAS WT	All study Population	Subpopulation KRAS WT	All study Population	Subpopulation KRAS WT	All study Population	Subpopulation KRAS WT
Study Population	Metastatic pancreatic cancer		Locally advanced or metastatic pancreatic cancer	Locally advanced or metastatic pancreatic cancer with KRAS WT	Locally advanced or metastatic pancreatic cancer	Locally advanced or metastatic pancreatic cancer with KRAS WT	Locally advanced or metastatic pancreatic cancer	Locally advanced or metastatic pancreatic cancer with KRAS WT
Comparator / Control Treatment	Gemcitabine Abraxane+Gemcitabine		Gemcitabine Nimotuzumab+Gemcitabine	Gemcitabine Nimotuzumab+Gemcitabine	Gemcitabine Nimotuzumab+Gemcitabine	Gemcitabine Nimotuzumab+Gemcitabine	Gemcitabine Nimotuzumab+Gemcitabine	Gemcitabine Nimotuzumab+Gemcitabine
2nd or 3rd option post study drug or comparator	gemcitabine group crossed over to receive a regimen that included nab-paclitaxel.		Unregulated treatment switching to 2nd or 3rd line was not taken into account during analysis		Treatment switching to 2nd line or 3rd line analysed by IPCW analysis		Treatment switching to 2nd line or 3rd line analysed by Extended Cox Model analysis	
Year of publication (ASCO)	2013		2013	2013	N/A	N/A	N/A	N/A
Sample size (total)	861		192	34	192	34	192	34
Efficacy Result (including p values)								
Median Overall Survival (treatment vs control)	8.5 vs 6.7 months (P<0.001, HR: 0.72)		8.6 vs 6.0 months (P=0.210, HR: 0.83)	12.2 vs 5.6 months (p-value=0.091, HR: 0.32)	8.43 vs 5.37 months (P=0.03 HR = 0.82)	7.5 vs 4 months (P=0.023, HR: 0.494)	7.3 vs 4.67 months (P=0.01, HR: 0.557); HR 0.671, p=0.011	11.65 vs 5.6 months (P=0.034, HR: 0.46); 11.65 vs 5.6, HR 0.46, p=0.034
Progression free survival (treatment vs control)	5.5 vs 3.7 months (P<0.001, HR: 0.69)		5.3 vs 3.5 months (P=0.077, HR: 0.76)	7.7 vs 2.4 months (p-value=0.194, HR: 0.61)	4.5 vs 3 months (P=0.004, HR = 0.704)	5 vs 3 months (P=0.065, HR: 0.575)	5.37 vs 2.6 months (P=0.0013, HR: 0.524)	7.1 vs 2 months (P=0.087, HR: 0.55)
Response Rate (treatment vs control)	23% vs 7% (P<0.001, HR: 3.19)		SD: 54.8% vs 43% (P=0.346)	Not analysed	Not analysed	Not analysed	Not analysed	Not analysed

Figure 2 (continued)

Safety Result (including p) values						
Side Effect	Grade 3 or 4 toxicities were observed: Patients with SAE (50% vs 43%)	no grade 3/4 toxicities were observed; SAE (58.1% vs 65.6%)	no grade 3/4 toxicities were observed; SAE (58.1% vs 65.6%)	no grade 3/4 toxicities were observed; SAE (58.1% vs 65.6%)	no grade 3/4 toxicities were observed; SAE (58.1% vs 65.6%)	
QOL	Not reported	Not significantly different	Not significantly different	Not significantly different	Not significantly different	
Side effect	Neutropenia (38% vs 27%)	Pyrexia (25.8% vs 12.9%) (p=0.04)	Pyrexia (25.8% vs 12.9%) (p=0.04)	Pyrexia (25.8% vs 12.9%) (p=0.04)	Pyrexia (25.8% vs 12.9%) (p=0.04)	
	fatigue (17% vs 7%)	Chills 17.7% vs 4.2% (p=0.01)	Chills (17.7 vs 4.2%) (p=0.01)	Chills (17.7 vs 4.2%) (p=0.01)	Chills 17.7% vs 4.2% (p=0.01)	
	Neutropathy (17% vs 1 %)					
References	Von Hoff DD, Ervin T, Arena FP, Chiorean GE, Infante J, et al. 2013. Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine. The New England Journal of Medicine 3689: 1691-1703	Dirk Strumberg, Beate Schultheis, Matthias Philip Ebert, A. Kerkhoff, Ralf Dieter Hofheinz, et al. (2013). Phase II, randomized, double-blind placebo-controlled trial of nimotuzumab plus gemcitabine compared with gemcitabine alone in patients (pts) with advanced pancreatic cancer (PC). 2013 ASCO Annual meeting				
Conclusion	In patients with metastatic pancreatic adenocarcinoma, nab-paclitaxel plus gemcitabine significantly improved overall survival, progression-free survival, and response rate, but rates of peripheral neuropathy and myelosuppression were increased.	This randomized study clearly showed that nimo in combination with gem is safe and well tolerated. The overall survival between Nimotuzumab+Gemcitabine and Gemcitabine treatment is not significantly different.	In KRAS WT sub-population, the clinical benefit is improved compared to general population, but the difference does not reach statistical significance.	Using IPCW model, significant difference of overall survival can be observed in Nomotuzumab treatment	Using IPCW model in subgroup of KRAS WT, improved overall survival is increased	There was a statistical significant difference in the overall survival when switch to 2nd line was considered
						In the analysis of subgroup of KRAS WT when 2nd line was considered, overall survival is significantly improved with increase of median OS of 6 months

Figure 3

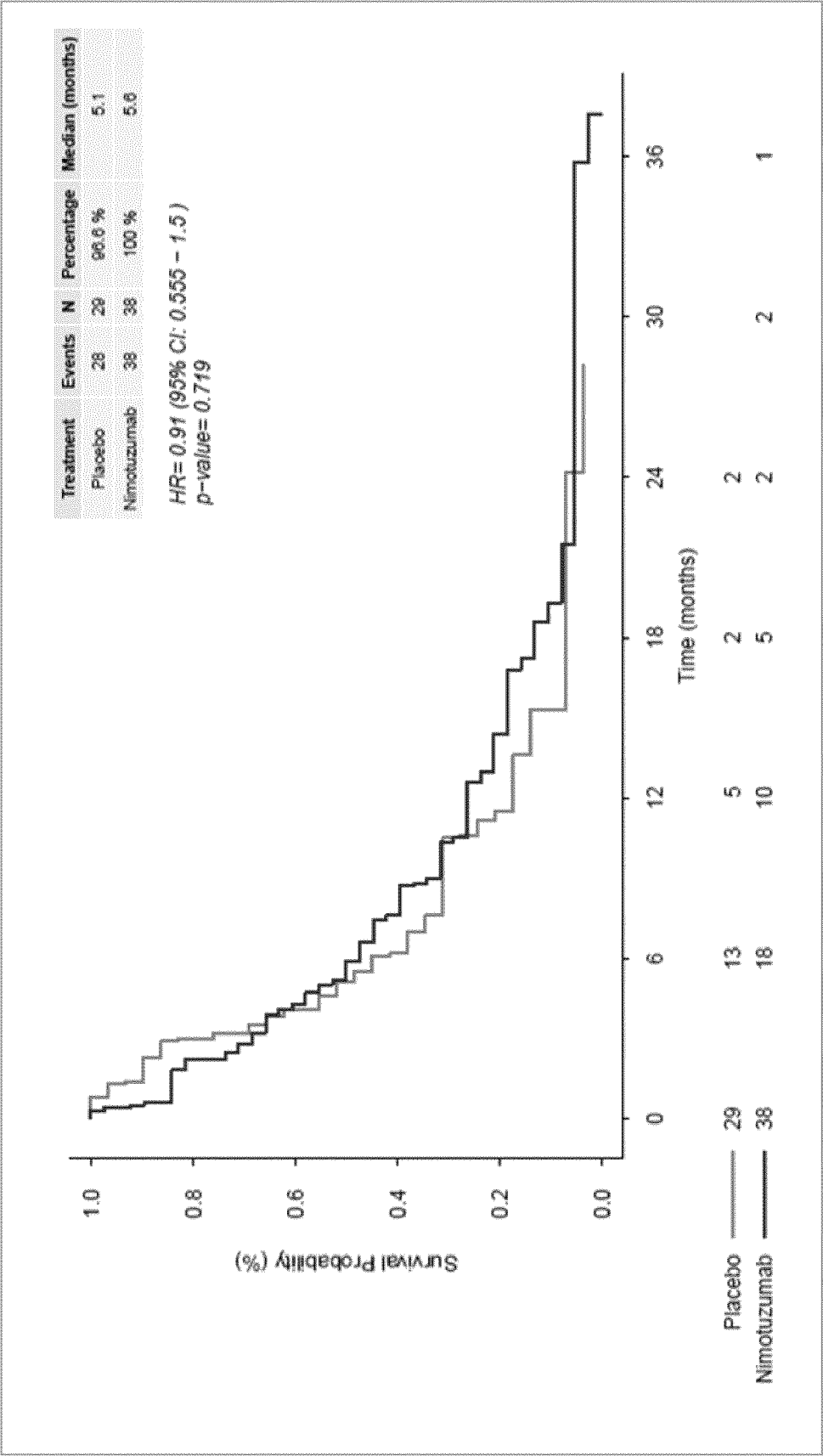


Figure 4

