

**Supplementary Table S1:** SIRP $\alpha$ , CD47 and EGFR expression levels on indicated cells expressed as the mean specific antibody binding capacity (sABC). N indicates the number of tests performed.

Cell line / Receptor	SIRP $\alpha$		CD47		EGFR (panitumumab)		EGFR (cetuximab)	
	Mean sABC	N	Mean sABC	N	Mean sABC	N	Mean sABC	N
SW48 (006)	< 3300 <sup>§</sup>	2	53681	5	104416	5	118262	5
SW48 (115)	< 3300 <sup>§</sup>	2	56096	5	98710	5	126366	5
SW48 BRAF V600E	< 3300 <sup>§</sup>	2	71094	2	47841	2	68095	2
SW48 KRAS G12D	< 3300 <sup>§</sup>	2	70397	2	74716	2	125488	2
SW48 KRAS G13D	< 3300 <sup>§</sup>	2	77390	2	143566	2	186522	2

§: Receptor expression is below the lowest calibration point of the Human IgG calibrator kit, namely 3300 receptors/cell.

**Supplementary Table S2:** Observed affinities ( $K_D$ -obs) for BYON4228-IgG1-L234A/L235A and BYON4228-IgG1 binding to Fc $\gamma$  Receptors.

Ligand	BYON4228-IgG1-L234A/L235A Observed affinities ( $K_D$ -obs)	SYD5664-IgG1* Observed affinities ( $K_D$ -obs)
Human Fc $\gamma$ RIIIa (CD16a)	15.1 $\mu$ M	2.6 $\mu$ M
Human Fc $\gamma$ RIIIb (CD16b)	> 16.7 $\mu$ M	7.4 $\mu$ M
Human Fc $\gamma$ RIIa (CD32a H131 or R131)	> 16.7 $\mu$ M	1.4 or 1.6 $\mu$ M
Human Fc $\gamma$ RIIb (CD32b)	> 16.7 $\mu$ M	6.5 $\mu$ M
Human Fc $\gamma$ RI (CD64)	> 1.67 $\mu$ M	2.5 nM

\* SYD5664 contains the variable domains of BYON4228 but has a wildtype IgG1 constant domain with wildtype effector functions.

**Supplementary Table S3:** BYON4228 PK in mice after single IV dose.

Parameter	huSIRP $\alpha_{BIT}$ mice			C57BL/6 mice
	3 mg/kg	10 mg/kg	30 mg/kg	3 mg/kg
$C_{max}$ ( $\mu$ g/mL)	44.2	197	581	45.2
AUC <sub>last</sub> (h* $\mu$ g/mL)	1340	9810	36700	3390

Last sample taken at 168 h

**Supplementary Table S4:** BYON4228 PK in mice after single IP dose.

Parameter	huSIRP $\alpha_{BIT}$ mice			C57BL/6 mice
	3 mg/kg	10 mg/kg	30 mg/kg	3 mg/kg
$C_{max}$ ( $\mu$ g/mL)	21.9	78.5	311	29.8
AUC <sub>last</sub> (h* $\mu$ g/mL)	940	8720	33400	3730

Last sample taken at 168 h

**Supplementary Table S5: BYON4228 PK in monkey after a single IV dose**

Parameters	1 mg/kg BYON4228	3 mg/kg BYON4228	10 mg/kg BYON4228	30 mg/kg BYON4228	100 mg/kg BYON4228
$t_{1/2}$ (h)	105	66.8	95.6	109	100
$C_{max}$ ( $\mu\text{g/mL}$ )	27.2	90.5	278	930	1740
$AUC_{last}$ ( $\text{h} \cdot \mu\text{g/mL}$ )	2010	5520	29100	131000	426000
$AUC_{inf}$ ( $\text{h} \cdot \mu\text{g/mL}$ )	2080	6190	30400	143000	449000
CL ( $\text{mL/h/kg}$ )	0.496	0.485	0.329	0.218	0.229
$V_{ss}$ ( $\text{mL/kg}$ )	55.8	47.0	44.2	37.6	41.5

Cynomolgus monkeys after single IV infusion of BYON4228, animals sampled for 3 weeks following dosing. Values are means of n=2, with one male and one female animal per dose group.

**Supplementary Movies:** Real-time phagocytosis was visualized using live-cell imaging. Panitumumab-opsonized (40 ng/mL) HT-29 tumor cells were labeled with pHrodo and co-incubated with unlabeled macrophages and BYON4228 (10  $\mu\text{g/mL}$ ). Images were taken every 3 minutes for 4 hours. The light-red tumor cells become bright red upon phagocytosis by macrophages.