Supplementary Table S1. Cell line sources and authentication.

Cell line	Provider	Date obtained	STR date
A-204	ATCC	February 27, 2014	July 29, 2014
A549	ATCC	October 22, 2003	July 27, 2016
A-673	ATCC	September 26, 2013	November 26, 2013
ABC-1	JCRB	June 19, 2013	September 16, 2013
AN3 CA	ATCC	July 29, 2013	December 12, 2013
BE(2)-C	ATCC	April 4, 2010	September 7, 2015
BT-549	ATCC	April 9, 2015	September 7, 2015
C2BBe1	ATCC	November 26, 2012	February 7, 2013
Caco-2	ATCC	September 13, 2004	August 22, 2014
Calu-6	ATCC	January 17, 2000	June 24, 2011
Caov-3	ATCC	April 4, 2013	May 22, 2013
Caov-4	ATCC	January 15, 2015	December 23, 2015
CL-14	DSMZ	January 2, 2013	April 20, 2013
COLO 201	ATCC	April 14, 2015	February 17, 2016
COLO 205	ATCC	February 21, 2003	May 4, 2011
D341 Med	ATCC	June 29, 2015	August 24, 2015
DLD-1	ATCC	December 13, 2002	June 12, 2015
DMS 114	ATCC	April 12, 2013	February 20, 2014
DMS 273	ECACC	November 12, 2013	June 6, 2014
DMS 53	ATCC	September 26, 2013	February 4, 2014
EFE-184	DSMZ	June 25, 2014	March 21, 2017
GEO	S. Pepe, University of Naples	April 15, 2008	Not authenticated
GP5d	ECACC	November 26, 2012	February 7, 2013
HCC2935	ATCC	August 5, 2015	September 22, 2015
HCC4006	ATCC	May 7, 2015	November 12, 2015
HCC-461	H. Greulich, Dana-Farber Cancer Institute	September 29, 2008	April 11, 2013
HCC-827	ATCC	March 7, 2014	October 31, 2014
HCT 116	ATCC	June 17, 2011	April 17, 2012
HCT-15	ATCC	December 9, 2002	July 31, 2013
HEC-1-A	ATCC	May 24, 2011	November 3, 2011
HEC-1-B	ATCC	January 17, 2014	June 12, 2014
Hep 3B2.1-7	ATCC	April 4, 2013	August 28, 2013
HL-60	ATCC	February 12, 2014	May 14, 2014
Hs 913T	ATCC	February 21, 2014	August 22, 2014
HT-1080	DSMZ	January 24, 2012	April 2, 2012
HT-29	ATCC	January 24, 2012	February 28, 2013
JHH-7	JCRB	March 22, 2013	April 24, 2013
KLE	ATCC	March 1, 2012	January 15, 2014
KYM-1	ATCC	July 2, 2013	August 12, 2013
LNCap.FGC	ATCC	April 25, 2013	June 26, 2013
LoVo	ATCC	April 11, 2013	May 23, 2013
LS 174T	ATCC	July 4, 2014	September 7, 2015
LS1034	ATCC	April 27, 2012	September 29, 2014
LS411N	ATCC	August 24, 2006	June 16, 2015
LS513	ATCC	September 23, 2011	April 17, 2014
Lu-134-A-H	JCRB	June 24, 2013	October 18, 2013
MCF7	DSMZ	March 19, 2014	October 9, 2014
MDA-MB-468	ATCC	June 14, 2014	October 9, 2014
MFE-280	DSMZ	February 5, 2014	April 28, 2014
MOLP-8	DSMZ	February 26, 2014	August 22, 2014
MV-4-11	ATCC	July 13, 2010	December 3, 2015
NCI-H1650	ATCC	January 9, 2013	March 20, 2013
NCI-H1975	ATCC	October 1, 2007	May 14, 2014
NCI-H2030	ATCC	March 19, 2013	September 7, 2015
NCI-H2085	ATCC	July 7, 2004	January 31, 2012
NCI-H2122	ATCC	May 7, 2013	May 23, 2013
NCI-H2887	H. Beug, Research Institute of Molecular Pathology	December 1, 2004	January 23, 2014
NCI-H3255	H. Beug, Research Institute of Molecular Pathology	December 15, 2006	May 14, 2014
NCI-H358	ATCC	March 6, 2013	February 26, 2015
NCI-H522	ATCC	May 14, 2013	November 20, 2015
NCI-H650	ATCC	June 12, 2013	September 13, 2013

NCI-H684	KCLB	January 8, 2014	July 29, 2014
NCI-H716	ATCC	June 22, 2011	November 18, 2011
NCI-H727	ATCC	April 4, 2014	October 29, 2014
NCI-H747	ATCC	October 20, 2012	September 7, 2015
OUMS-23	JCRB	March 1, 2011	August 24, 2011
OV-90	ATCC	March 13, 2012	December 23, 2015
OVKATE	JCRB	May 16, 2014	January 9, 2015
OVXF1023	Oncotest	October 7, 2014	September 7, 2015
PC-9	ECACC	October 27, 2015	December 3, 2015
RD	ATCC	June 6, 2000	April 2, 2012
RD-ES	ATCC	October 8, 2010	September 7, 2015
RH-41	DSMZ	March 18, 2013	April 24, 2013
RKO	ATCC	March 7, 2014	May 14, 2014
RL95-2	ATCC	July 3, 2013	September 23, 2013
RMG-I	JCRB	April 7, 2012	August 9, 2012
SJCRH30	ATCC	January 17, 2014	September 3, 2014
SJSA-1	ATCC	January 8, 2008	May 29, 2013
SK-CO-1	ATCC	February 21, 2014	September 3, 2014
SK-N-AS	ATCC	March 6, 2014	June 6, 2014
SK-N-DZ	ATCC	May 9, 2008	December 23, 2015
SK-OV-3	ATCC	July 11, 2013	November 26, 2013
SK-UT-1	ATCC	July 18, 2013	October 18, 2013
SNU-1033	KCLB	July 11, 2013	December 18, 2013
SNU-C4	KCLB	April 11, 2013	May 6, 2013
SW1417	ATCC	July 25, 2014	December 15, 2014
SW1463	ATCC	June 12, 2013	December 11, 2014
SW403	ATCC	April 15, 2008	June 9, 2011
SW48	ATCC	August 21, 2014	May 13, 2015
SW480	ATCC	May 16, 2001	August 24, 2015
SW620	ATCC	April 3, 2013	August 12, 2013
SW837	ATCC	April 21, 2011	November 18, 2011
SW948	ATCC	April 18, 2013	May 30, 2013
T84	ATCC	July 1, 2012	September 28, 2012
TE 381.T	ATCC	May 10, 2011	April 2, 2012
TOV-112D	ATCC	May 25, 2009	May 14, 2014
TOV-21G	ATCC	April 28, 2009	April 17, 2012
WiDr	ATCC	March 8, 2010	April 17, 2014

NOTE: The source and date when each cell line was obtained are indicated. Cell lines were most recently authenticated by STR analysis at Boehringer Ingelheim on the indicated date. The cell line GEO was not authenticated, owing to the lack of a published STR reference.

Abbreviations: ATCC, American Type Culture Collection; DSMZ, German Collection of Microorganisms and Cell Cultures; ECACC, Culture Collections of Public Health England; JCRB, Japanese Collection of Research Bioresources Cell Bank; KCLB, Korean Cell Line Bank.

Supplementary Table S2. Mutual exclusivity of alterations in patient CRC samples.

	APC	***BRAF***	***CTNNB1***	***IGF2***	***KRAS***	***NRAS***	***PIK3CA***	***PTEN***	***SMAD4***	***TP53***
APC	NA	**5.83×10^{-6}**	0.114	0.15	0.992	0.835	0.645	0.909	0.347	0.439
BRAF	**5.83×10^{-6}**	NA	0.175	**0.0339**	**0.00239**	0.0512	0.967	0.756	0.617	**0.00952**
CTNNB1	0.114	0.175	NA	0.996	0.7	0.954	0.978	0.678	0.401	0.0833
IGF2	0.15	**0.0339**	0.996	NA	0.326	0.426	0.0646	**0.0208**	0.088	**0.0294**
KRAS	0.992	**0.00239**	0.7	0.326	NA	0.198	0.838	0.465	0.838	0.185
NRAS	0.835	0.0512	0.954	0.426	0.198	NA	0.613	0.905	0.903	0.502
PIK3CA	0.645	0.967	0.978	0.0646	0.838	0.613	NA	0.514	0.465	**0.0436**
PTEN	0.909	0.756	0.678	**0.0208**	0.465	0.905	0.514	NA	0.988	0.16
SMAD4	0.347	0.617	0.401	0.088	0.838	0.903	0.465	0.988	NA	0.194
TP53	0.439	**0.00952**	0.0833	**0.0294**	0.185	0.502	**0.0436**	0.16	0.194	NA

NOTE: Exclusivity of alterations in the indicated genes from CRC patient samples from Fig. 1B. Pairs with a *P* value < 0.05 (marked in bold) were considered mutually exclusive. Only the most common missense mutations were analyzed for *PIK3CA* (exons 9 and 20), *BRAF* (codon 600), *KRAS* (codons 12, 13, 61 and 146) and *NRAS* (codons 12, 13 and 61).

Abbreviations: NA, not applicable.

Supplementary Table S3. Co-occurrence of alterations in CRC patient samples.

	APC	***BRAF***	***CTNNB1***	***IGF2***	***KRAS***	***NRAS***	***PIK3CA***	***PTEN***	***SMAD4***	***TP53***
APC	NA	1	0.886	0.85	**0.00798**	0.165	0.355	0.0908	0.653	0.561
BRAF	1	NA	0.825	0.966	0.998	0.949	**0.0332**	0.244	0.383	0.99
CTNNB1	0.886	0.825	NA	**0.00377**	0.3	**0.0463**	**0.0216**	0.322	0.599	0.917
IGF2	0.85	0.966	**0.00377**	NA	0.674	0.574	0.935	0.979	0.912	0.971
KRAS	**0.00798**	0.998	0.3	0.674	NA	0.802	0.162	0.535	0.162	0.815
NRAS	0.165	0.949	**0.0463**	0.574	0.802	NA	0.387	0.0945	0.0966	0.498
PIK3CA	0.355	**0.0332**	**0.0216**	0.935	0.162	0.387	NA	0.486	0.535	0.956
PTEN	0.0908	0.244	0.322	0.979	0.535	0.0945	0.486	NA	**0.0121**	0.84
SMAD4	0.653	0.383	0.599	0.912	0.162	0.0966	0.535	**0.0121**	NA	0.806
TP53	0.561	0.99	0.917	0.971	0.815	0.498	0.956	0.84	0.806	NA

NOTE: Co-occurrence of alterations in the indicated genes from CRC patient samples from Fig. 1B. Pairs with a *P* value < 0.05 (marked in bold) were considered to co-occur. Only the most common missense mutations were analyzed for *PIK3CA* (exons 9 and 20), *BRAF* (codon 600), *KRAS* (codons 12, 13, 61 and 146) and *NRAS* (codons 12, 13 and 61).

Abbreviations: NA, not applicable.

Supplementary Table S4. *In vitro* sensitivity of CRC cell lines to BI 885578, BMS-754807 and docetaxel.

Cell Line	BI 885578 GI_{50} (nmol/L)	BMS-754807 GI_{50} (nmol/L)	Docetaxel GI_{50} (nmol/L)	IGF2 (TPM)	IGF2 Classification
LS513	14	31	1	1	Low
LS1034	22	92	3	1649	High
C2BBe1	24	83	2	410	High
SNU-1033	27	12	2	281	High
WiDr	27	183	8	66	Low
SW948	29	82	3	1	Low
GEO	31	54	4	683	High
CL-14	31	83	4	3223	High
NCI-H684	33	104	9	1433	High
SK-CO-1	146	499	4	1	Low
SW48	823	972	2	1	Low
SW837	1010	1365	8	2	Low
T84	1159	1737	2	1	Low
SNU-C4	1279	3759	7	1	Low
SW480	1333	> 10000	3	61	Low
COLO 205	1461	4215	2	1	Low
NCI-H716	1920	573	ND	1	Low
SW1417	1937	3163	4	1	Low
RKO	1992	5858	3	1	Low
LS 174T	2618	3833	5	1	Low
SW403	2684	1813	4	1	Low
HCT-15	3674	7499	ND	1	Low
HCT 116	3464	5878	6	11	Low
LS411N	3474	> 10000	5	1	Low
NCI-H747	3680	> 10000	1	3	Low
OUMS-23	3708	> 10000	7	67	Low
COLO 201	4110	> 10000	5	2	Low
SW620	4406	4497	6	8	Low
DLD-1	5148	> 10000	6	4	Low
SW1463	7676	> 10000	4	1	Low
GP5d	> 10000	> 10000	ND	112	High
HT-29	> 10000	> 10000	5	32	Low
LoVo	> 10000	> 10000	2	5	Low

NOTE: Cell lines are sorted according to BI 885578 GI_{50} values. $IGF2^{high}$ = TPM ≥ 72. $IGF2^{low}$ = TPM < 72.

Abbreviations: ND, not determined.

Supplementary Table S5. *In vitro* sensitivity of non-CRC cell lines to BI 885578.

Cell Line	Tumor type	IGF2 (TPM)	IGF2 Classification	BI 885578 GI_{50} (nmol/L)	Sensitivity Classification
TE 381.T	RMS	1299	High	7	Sensitive
MCF7	Breast carcinoma	2	Low	8	Sensitive
D341 Med	Medulloblastoma	2	Low	10	Sensitive
SJCRH30	RMS	1790	High	11	Sensitive
SK-N-DZ	Neuroblastoma	4	Low	15	Sensitive
HL-60	AML	1	Low	15	Sensitive
Lu-134-A-H	SCLC	407	High	16	Sensitive
NCI-H727	NSCLC	3167	High	17	Sensitive
OV-90	OC	354	High	17	Sensitive
OVKATE	OC	1364	High	19	Sensitive
RD-ES	Ewing´s sarcoma	5	Low	20	Sensitive
ABC-1	NSCLC	4644	High	23	Sensitive
BE(2)-C	Neuroblastoma	1033	High	25	Sensitive
OVXF1023	OC	1942	High	33	Sensitive
RH-41	RMS	1427	High	35	Sensitive
MOLP-8	Multiple myeloma	1	Low	43	Sensitive
A549	NSCLC	4	Low	61	Sensitive
MV-4-11	AML	1	Low	108	Sensitive
RD	RMS	3315	High	140	Sensitive
JHH-7	HCC	7597	High	254	Sensitive
Hep 3B2.1-7	HCC	3984	High	442	Sensitive
SK-N-AS	Neuroblastoma	666	High	477	Sensitive
A-673	Ewing´s sarcoma	1	Low	578	Resistant
NCI-H358	NSCLC	5	Low	583	Resistant
Hs 913T	Fibrosarcoma	3	Low	723	Resistant
LNCap.FGC	Prostate carcinoma	1	Low	944	Resistant
HT-1080	Fibrosarcoma	2	Low	1056	Resistant
NCI-H2887	NSCLC	4	Low	1108	Resistant
AN3 CA	Uterus carcinoma	1	Low	1131	Resistant
HEC-1-A	Uterus carcinoma	1	Low	1131	Resistant
Caov-4	OC	229	High	1209	Resistant
SK-UT-1	Leiomyosarcoma	6	Low	1448	Resistant
NCI-H2085	NSCLC	441	High	1868	Resistant
Calu-6	NSCLC	72	High	2043	Resistant
HCC2935	NSCLC	7	Low	2202	Resistant
KLE	Uterus carcinoma	22	Low	2468	Resistant
NCI-H2030	NSCLC	84	High	2740	Resistant
A-204	RMS	17	Low	3094	Resistant
SJSA-1	Bone sarcoma	94	High	3500	Resistant
NCI-H2122	NSCLC	1	Low	3629	Resistant
NCI-H522	NSCLC	4	Low	3832	Resistant
HCC4006	NSCLC	3	Low	4256	Resistant
SK-OV-3	OC	1	Low	4423	Resistant
TOV-112D	OC	1	Low	4578	Resistant
NCI-H3255	NSCLC	1	Low	5682	Resistant
MFE-280	Uterus carcinoma	5	Low	6627	Resistant
NCI-H650	NSCLC	137	High	> 10000	Resistant

RL95-2	Uterus carcinoma	112	High	> 10000	Resistant
DMS 114	SCLC	18	Low	> 10000	Resistant
EFE-184	Uterus carcinoma	5	Low	> 10000	Resistant
Caov-3	OC	2	Low	> 10000	Resistant
HCC-827	NSCLC	2	Low	> 10000	Resistant
TOV-21G	OC	2	Low	> 10000	Resistant
BT-549	Breast carcinoma	1	Low	> 10000	Resistant
DMS 273	SCLC	1	Low	> 10000	Resistant
DMS 53	SCLC	1	Low	> 10000	Resistant
HCC-461	NSCLC	1	Low	> 10000	Resistant
HEC-1-B	Uterus carcinoma	1	Low	> 10000	Resistant
KYM-1	RMS	1	Low	> 10000	Resistant
MDA-MB-468	Breast carcinoma	1	Low	> 10000	Resistant
NCI-H1650	NSCLC	1	Low	> 10000	Resistant
NCI-H1975	NSCLC	1	Low	> 10000	Resistant
PC-9	NSCLC	2	Low	> 10000	Resistant
RMG-I	OC	1	Low	> 10000	Resistant

NOTE: Data corresponds to Fig. 6A. Cell lines are sorted according to BI 885578 GI_{50} values. $IGF2^{high}$ = TPM ≥ 72. $IGF2^{low}$ = TPM < 72. BI 885578-sensitive = GI_{50} < 500 nmol/L. BI 885578-resistant = GI_{50} > 500 nmol/L.

Supplementary Figure Legends

Supplementary Figure S1. IGF2 expression in matching colon adenocarcinoma and normal colon samples. IGF2 gene expression was analyzed in 43 matching colon adenocarcinoma and normal colon biopsies obtained from Indivumed GmbH.

Supplementary Figure S2. Expression of IGF1R and Akt proteins in CRC cell lines. Lysates from CRC cell lines cultured *in vitro* in fully-supplemented culture medium were examined by ELISA for levels of IGF1R (A) and Akt (B) proteins. For each assay, mean values ± standard deviations are presented, which were determined from three or more replicates. The cell lines are sorted according to IGF2 expression levels. $IGF2^{high}$ = TPM ≥ 72. $IGF2^{low}$ = TPM < 72.

Supplementary Figure S3. Effect of BI 885578 on phosphorylation of IGF1R and Akt in CRC xenograft tumors. C2BBe1 and SW48 tumor bearing mice were treated for 7 days with vehicle control or BI 885578 (40 mg/kg). Tumors were excised 6 h following the last dose. Tumor lysates were examined for levels of phospho-Akt or phospho-IGF1R using Bio-Plex assays. IGF1R and Akt protein levels were assessed by ELISA. For each assay, mean values ± standard deviations are presented, which were determined from 4 tumors per treatment group. * $P < 0.05$ for treated versus control group.

Supplementary Figure S4. Tumor growth kinetics and efficacy of the combination of BI 885578 with anti-VEGF-A in CRC xenograft models. Data corresponds to the xenograft experiments shown in Fig. 4. Mean tumor volumes ± standard deviations were monitored for each treatment group (n=7) on the days indicated by a data point.

Supplementary Figure S5. Mouse body weight change kinetics under treatment with BI 885578 and anti-VEGF in the CRC xenograft model GEO. Data corresponds to the GEO xenograft shown in Fig. 4 and Supplementary Fig. S4. Mean percentage body weight change relative to baseline ± standard deviations are demonstrated for each treatment group (n=7).

Supplementary Figure S6. Combination of BI 885578 with anti-tumor agents in GEO xenografts. A, GEO tumor-bearing mice (7 per group) were treated with BI 885578 (40 or 20 mg/kg), irinotecan (40 mg/kg), 5-FU/folinic acid (100 mg/kg and 20 mg/kg, respectively) and the indicated combinations. B, GEO tumor-bearing mice (7 per group) were treated with BI 885578 (40 or 20 mg/kg), nintedanib (50 mg/kg), oxaliplatin (15 mg/kg) and the indicated combinations. Relative tumor volume to baseline for each mouse and TGI data for each group are indicated for the last day of treatment. The indicated *P* values refer to the comparison of TGI data from the combination versus the highest single agent (HSA). *BI 885578 was used in the combination at 20 mg/kg.

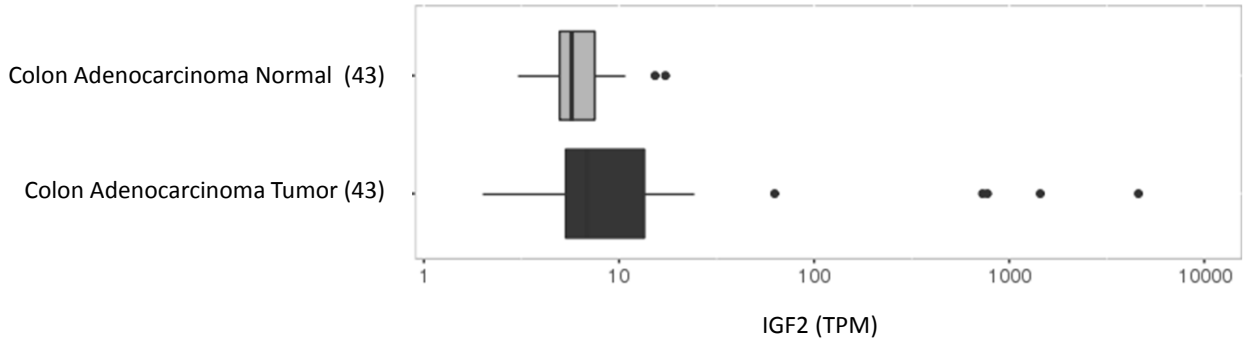
Supplementary Figure S7. Mouse body weight change kinetics under treatment with BI 885578 and anti-tumor agents in the CRC xenograft model GEO. A, Body weight change data corresponding to the GEO xenograft shown in Supplementary Fig. S6A. B, Body weight change data correspond to the GEO xenograft shown in Supplementary Fig. S6B. Mean percentage body weight change relative to baseline ± standard deviations are demonstrated for each treatment group (n=7).

Supplementary Figure S8. Effect of BI 885578 on expression of HIF1α by CRC cell lines. GEO, C2BBe1, SW48 and LoVo cells were treated *in vitro* for 24 h with BI 885578, dose-titrated between 500 – 0 nmol/L, in fully-supplemented culture medium. Cell lysates were analyzed by ELISA for expression of HIF1α.

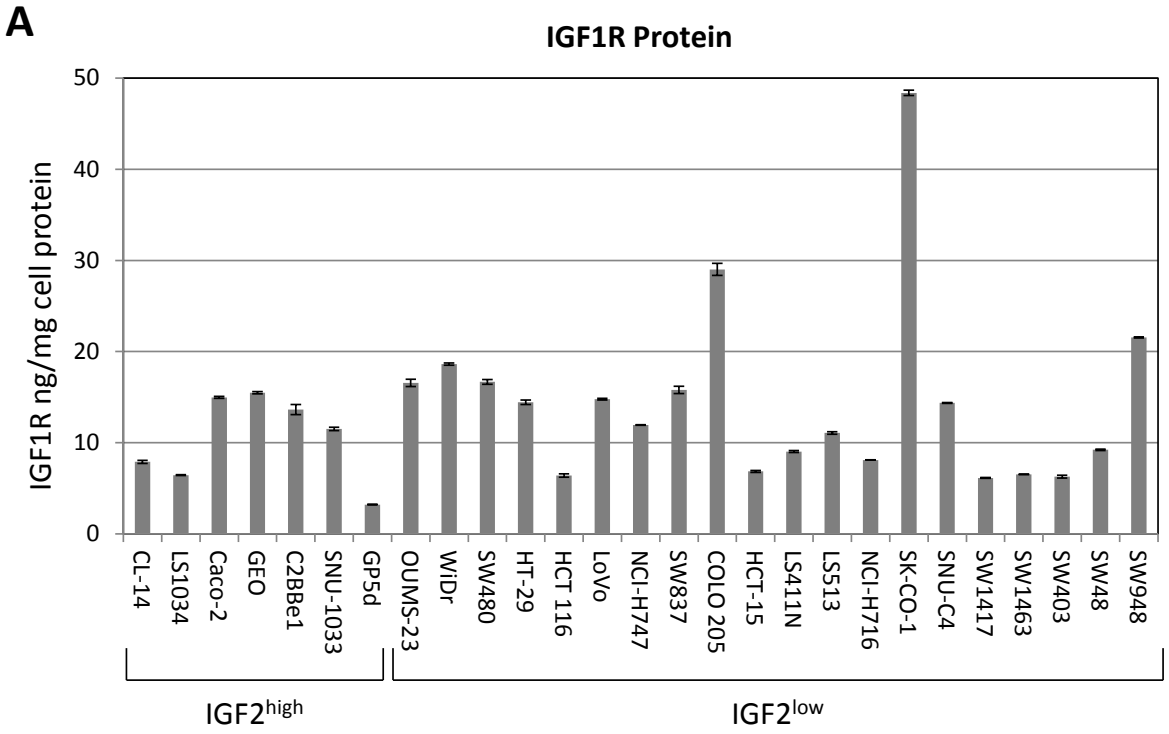
Supplementary Figure S9. Effect of BI 885578 and IGF2 on expression of VEGF-A by CRC cell lines. A, GEO and SW48 cells were treated *in vitro* for 24 h with BI 885578 (500 nmol/L) or an equivalent volume of DMSO (control) in fully-supplemented culture medium. Cell lysates were analyzed by ELISA for expression of VEGF-A. Mean values ± standard deviations are presented, which were determined from duplicate samples. B, GEO and SW48 cells were treated *in vitro* with 100 ng/ml IGF2 or an equivalent volume of PBS (control) for 24 h in fully-supplemented culture medium. Cell lysates were analyzed for VEGF-A levels as above. Data are presented as the fold-level of VEGF-A relative to control, which were determined from duplicate samples.

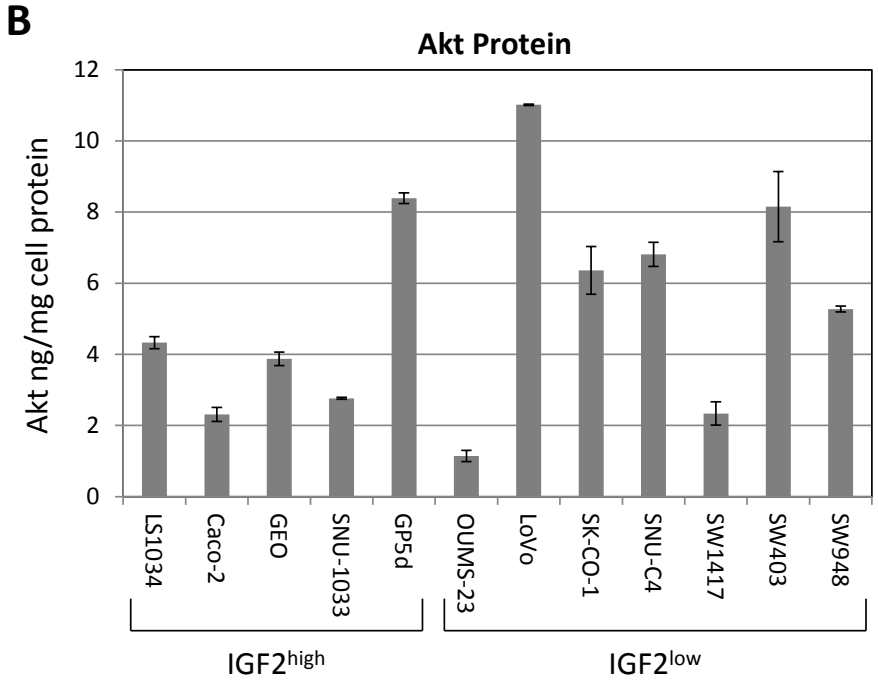
Supplementary Figure S10. Expression of IGF1R in non-CRC cell lines. Lysates from the indicated cell lines cultured *in vitro* in fully-supplemented culture medium were examined by ELISA for expression of IGF1R. Mean values ± standard deviations are presented, which were determined from three or more replicates. The cell lines are sorted according to IGF2 expression levels. $IGF2^{high}$ = TPM ≥ 72. $IGF2^{low}$ = TPM < 72.

Supplementary Figure S1

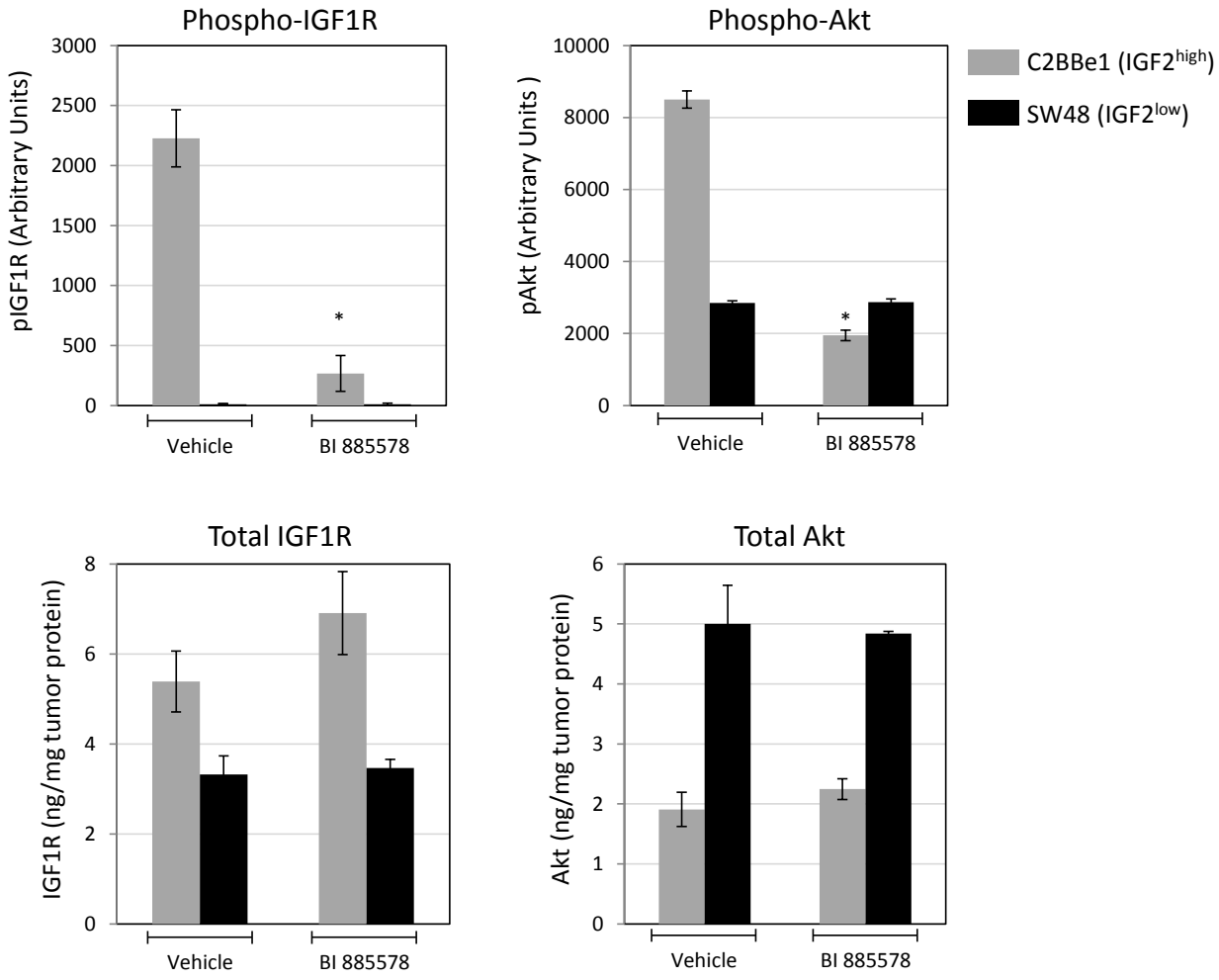


Supplementary Figure S2

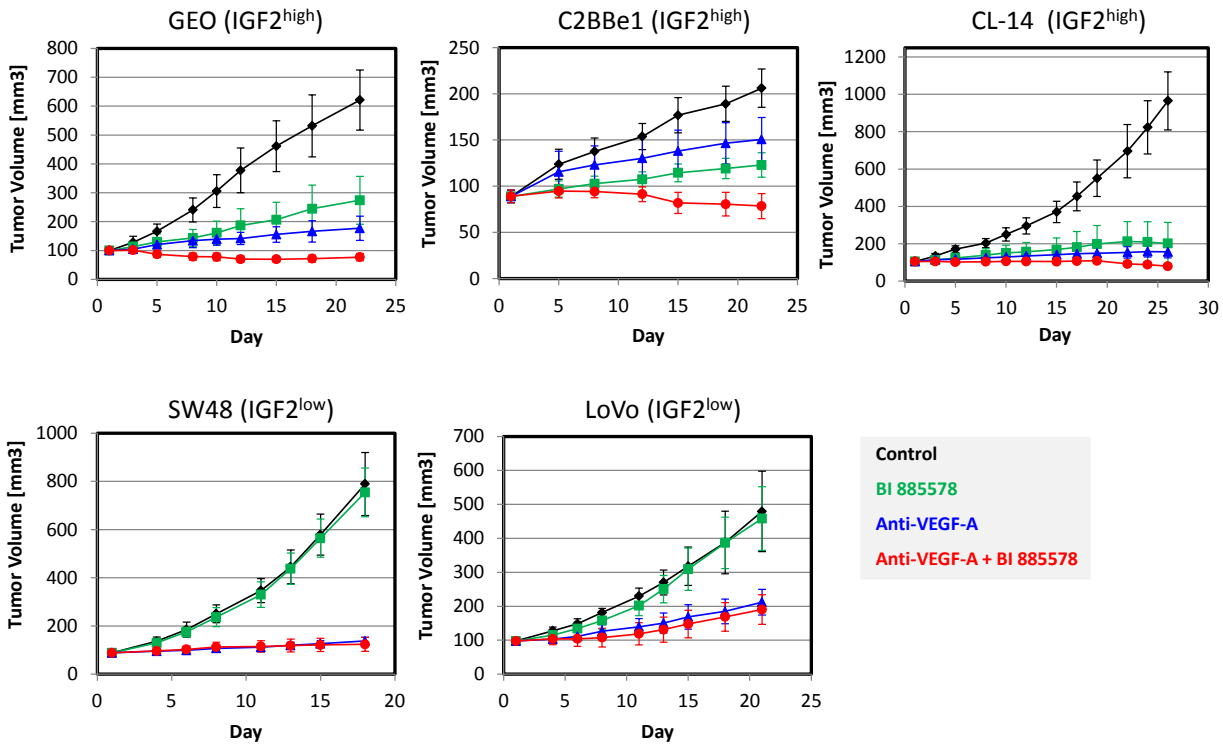




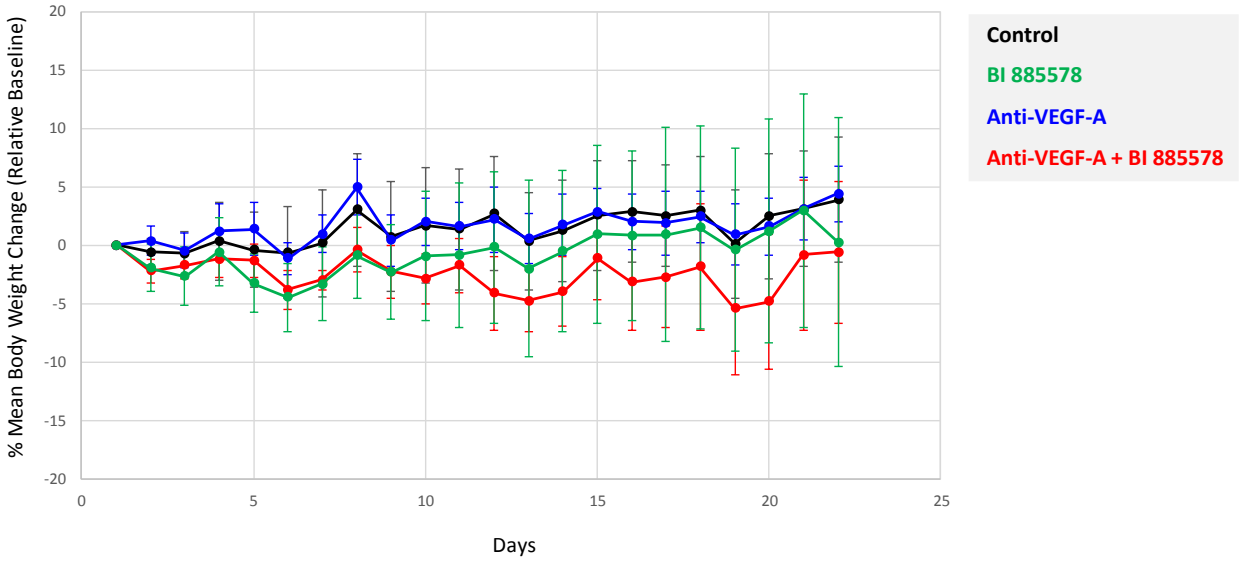
Supplementary Figure S3



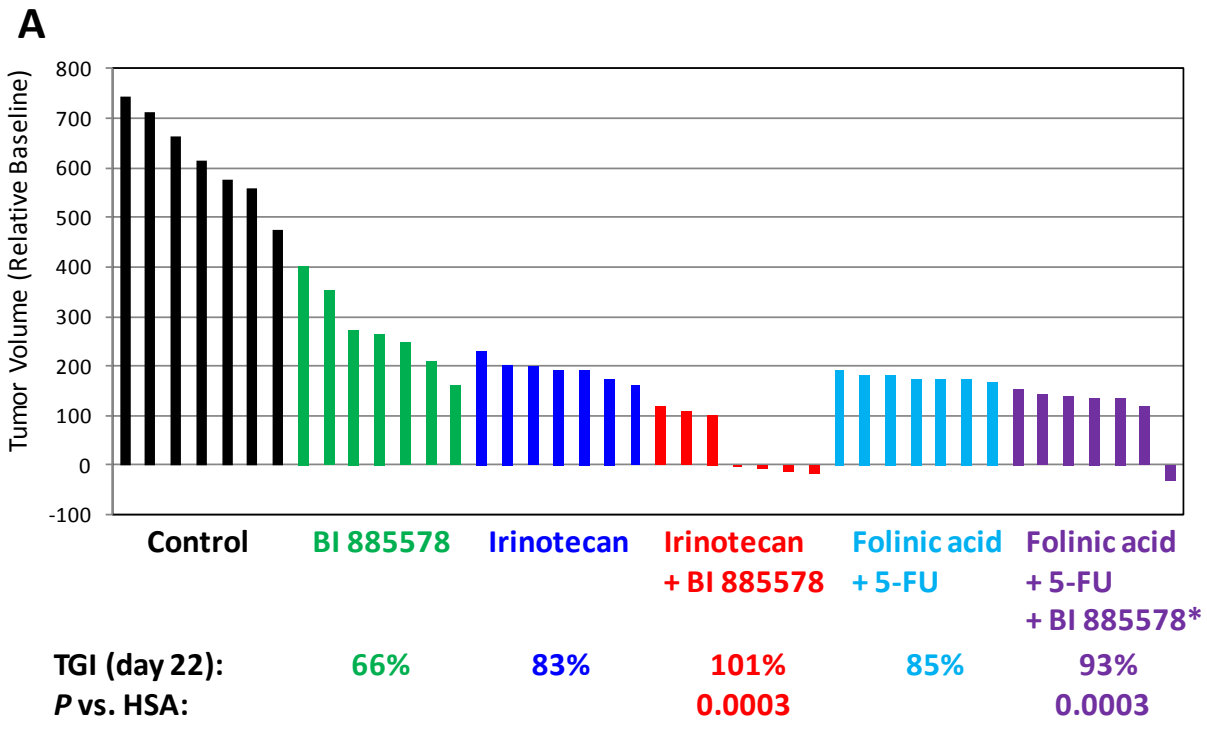
Supplementary Figure S4

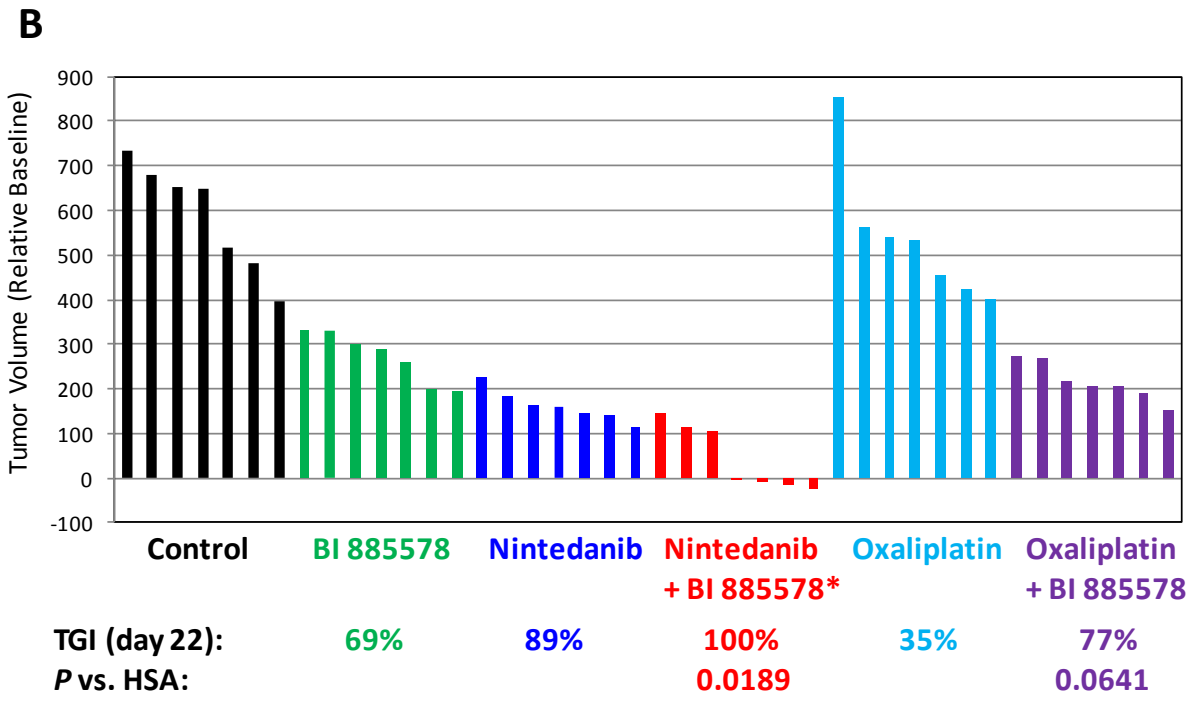


Supplementary Figure S5

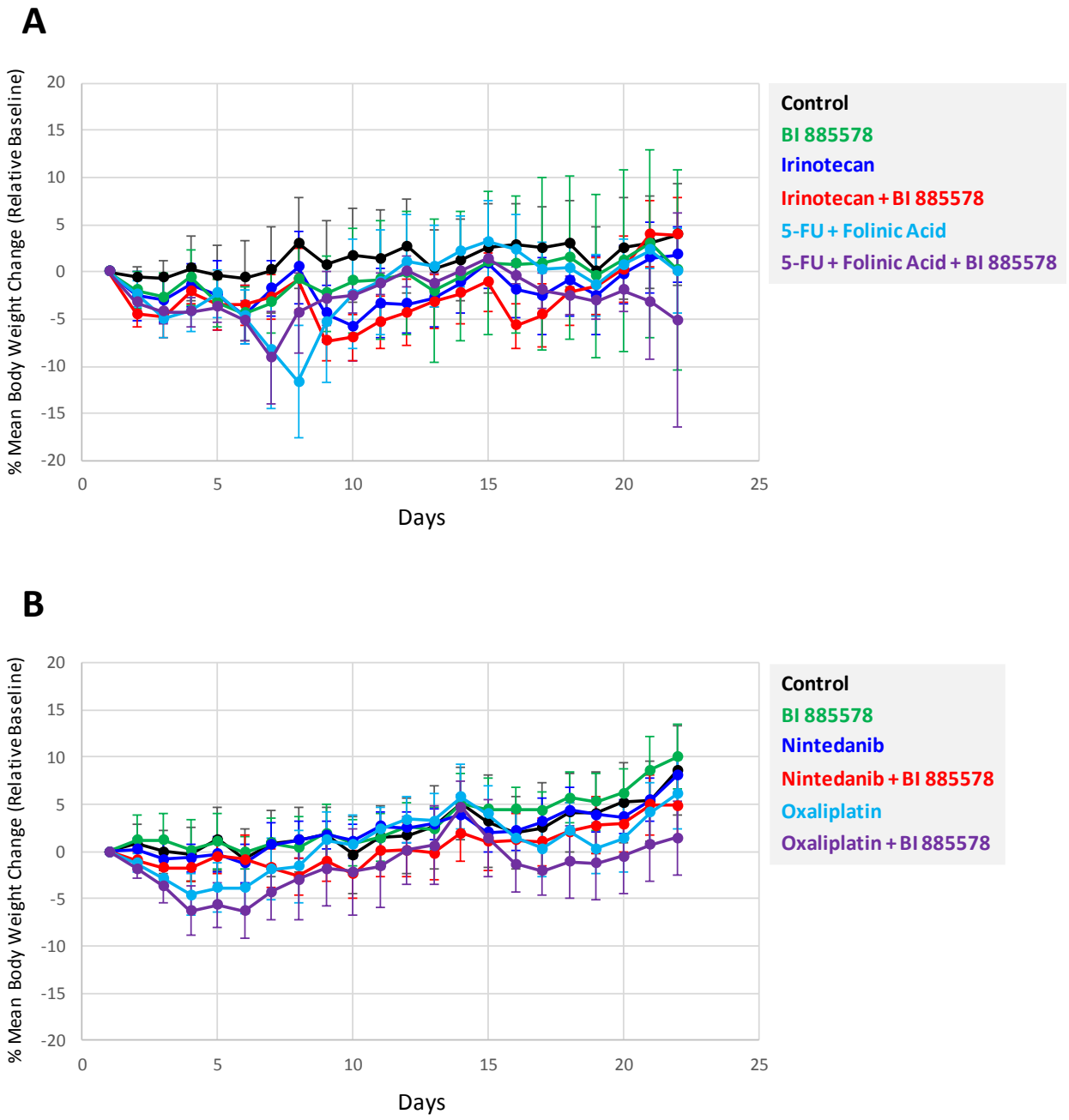


Supplementary Figure S6





Supplementary Figure S7



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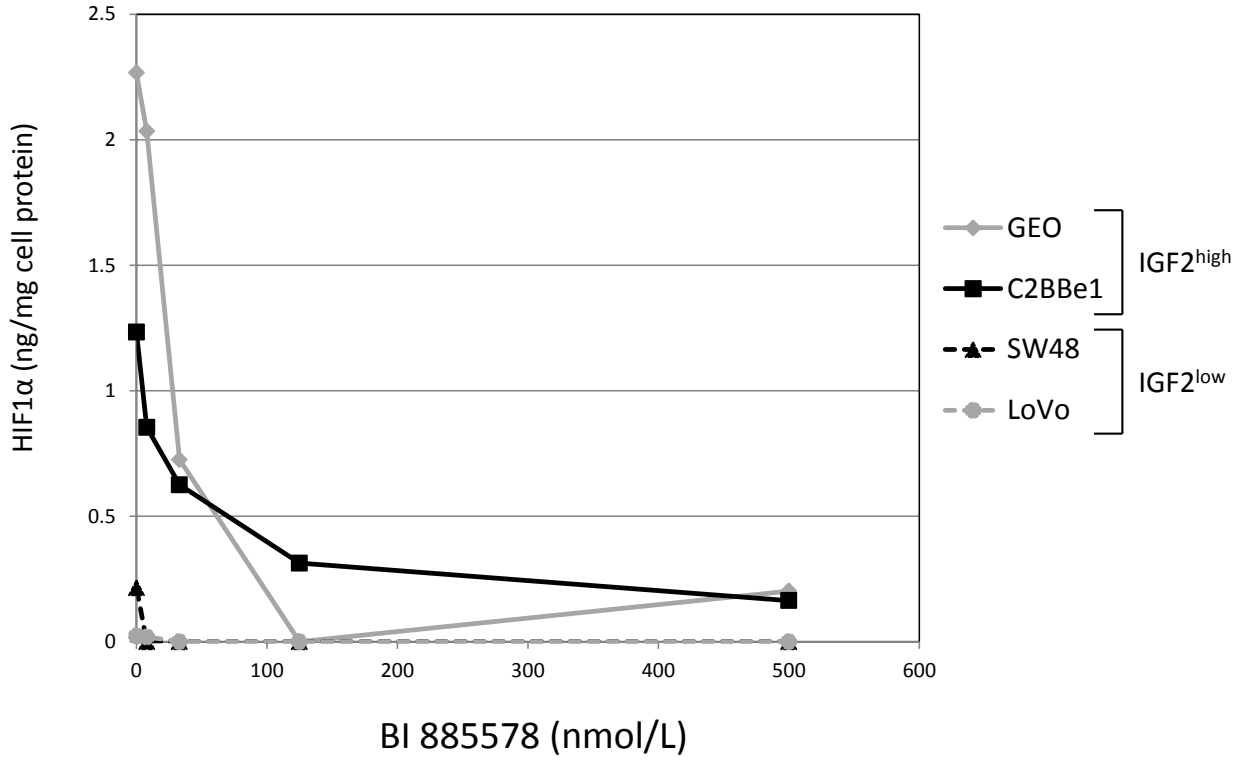
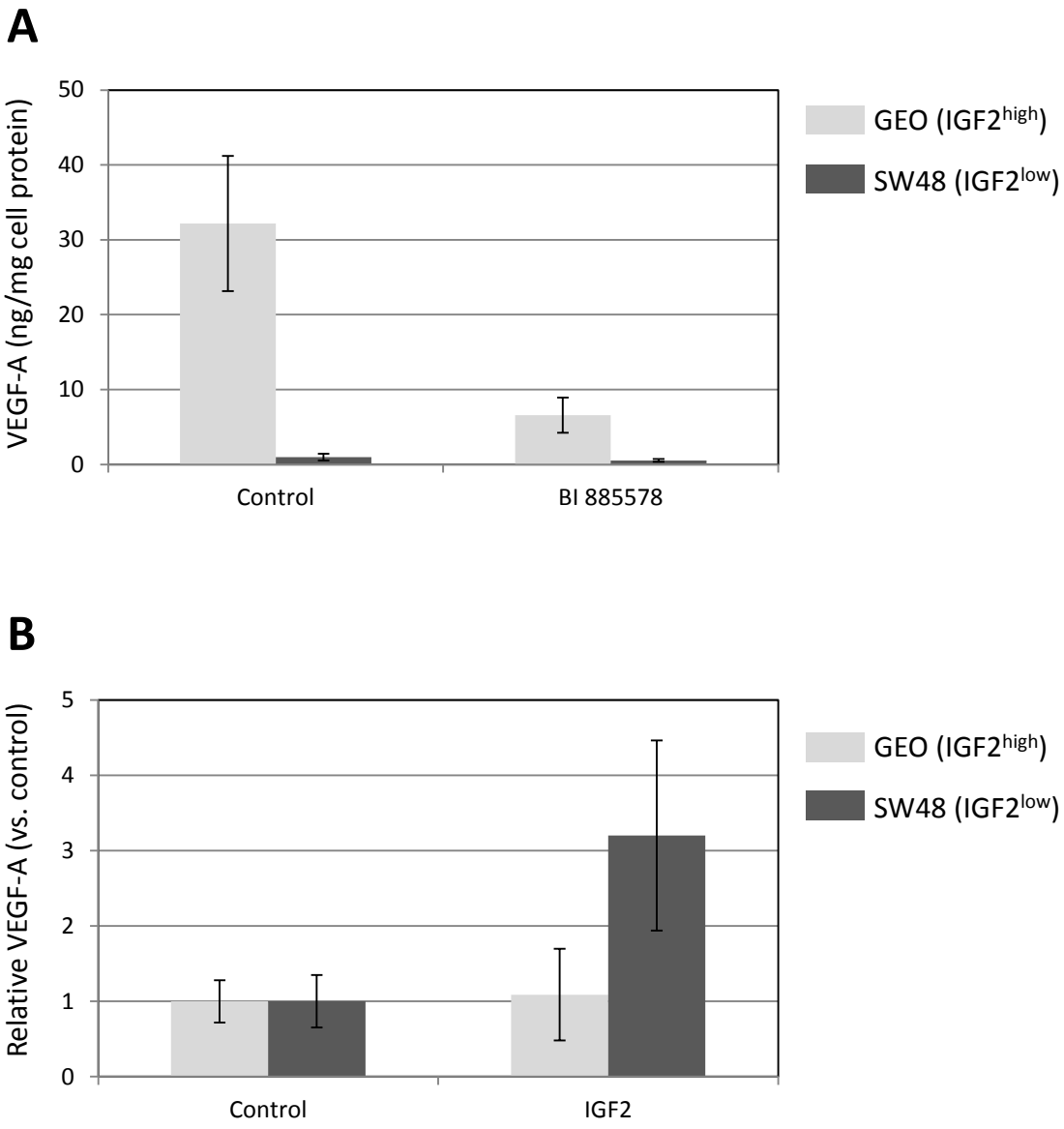


Supplementary Figure S9



Supplementary Figure S10