Supplementary materials

Supplementary materials and methods: FGFR expression and copy number analysis

We analyzed copy numbers from exome sequencing with two modifications. First, in the absence of a matched normal sample from a patient, a collection of normal blood samples from other male patients was used as a reference. Specifically, per-exon coverage was summed across 16 exome libraries prepared from normal blood specimens from male patients; per-exon coverage quantifications in the tumor sample were compared with these pooled normal quantifications. Second, presumably because the average ploidy in the tumor samples was greater than 2, median centering was not sufficient to appropriately normalize the $\log_2$ coverage ratios. Thus, all $\log_2$ coverage ratios were perturbed by a constant value (–0.45) representing a peak of the distribution of coverage ratios.

To choose cutoffs for gain and loss, we assumed that a tumor sample came from a tumor/non-tumor mixture with an unknown tumor fraction between 70% and 100%. For tumor fractions in this range, regions of one-copy loss would then be expected to have $\log_2$ coverage ratios less than $\log_2(0.7*1 + 0.3*2) - 1 = -0.62$ and regions of two-copy loss would be expected to have $\log_2$ coverage ratios less than $\log_2(0.7*0 + 0.3*2) - 1 = -1.74$. Nine segments comprised 1794 total exons with $\log_2$ coverage ratios between –1.74 and –0.62. The weighted mean of these $\log_2$ coverage ratios, weighted by the number of exons in each segment, was –0.89 (assuming that segments representing regions of one-copy loss yields a tumor fraction estimate of 92%). Using this estimate, the segment means were transformed into estimates of the number of copies per tumor cell and rounded to the nearest integer to arrive at an estimated number of copies.

Per-exon coverage values were extracted using BEDTools version 2.17.0 software. Downstream segmentation analysis was done with R version 2.15.1 software with the Circular Binary Segmentation algorithm as implemented in the DNAcopy package version 1.32.0.

Supplementary Figures

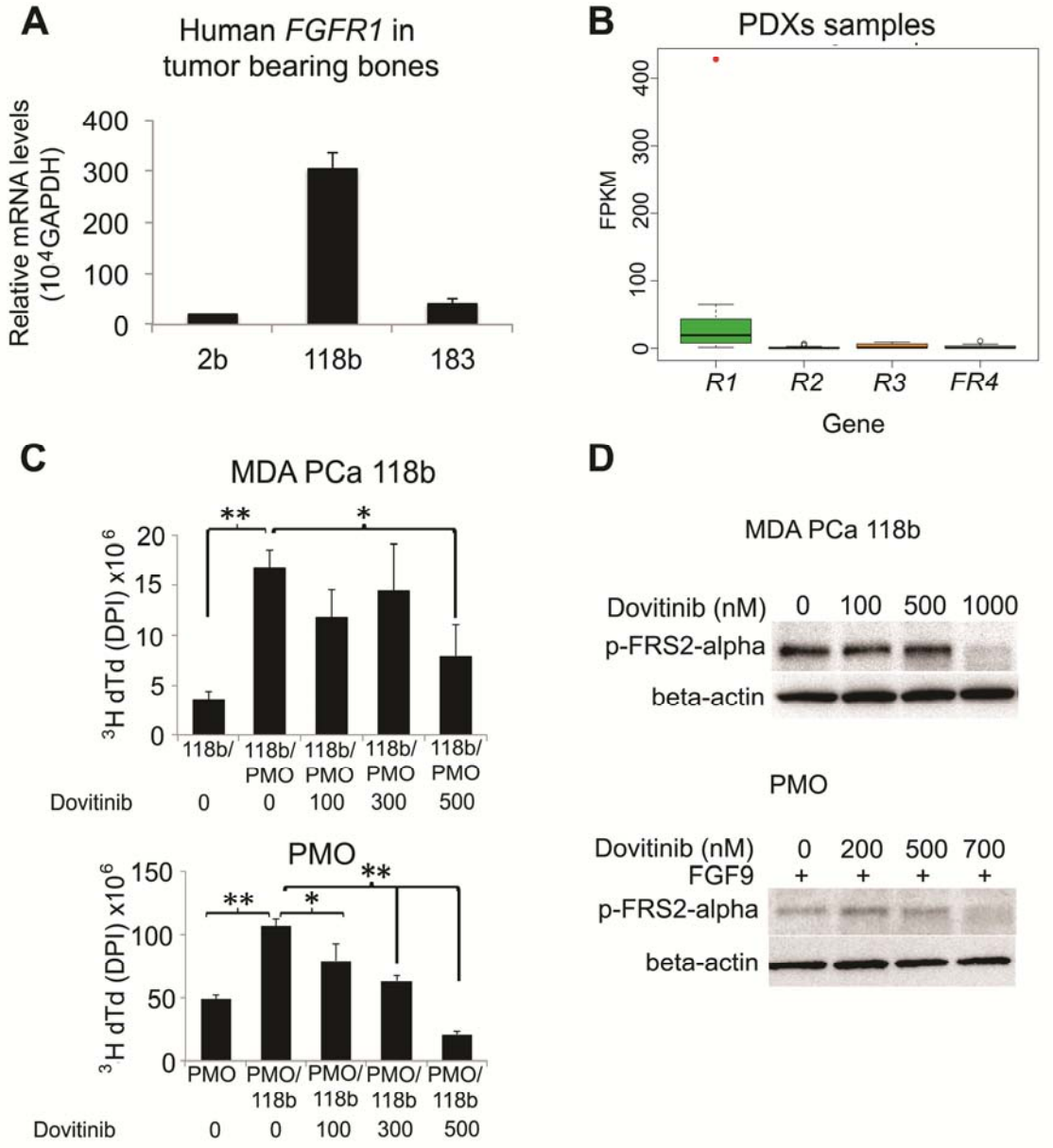


Fig. S1. *FGFR* gene family expression in PDXs and the effect of dovitinib on MDA PCa 118b cells *in vitro*. (**A**) Relative expression of human *FGFR1* mRNA in tumor-bearing femurs as assessed by real time RT-PCR analysis (n=6). RNA was isolated from the PCa-bearing femurs of mice by using human-specific primers. 2b, MDA PCa 2b; 118b, MDA PCa 118b; 183, MDA PCa 183. Error bars indicate standard error of the mean (SEM)**.** (**B**) Boxplots showing RNA sequencing gene expression values (RPKM) for *FGFR* family genes in 16 PCa PDX samples. The FGFR1 outlier, shown as a red dot, is from PDX sample MDA PCa 118b. (**C**) ^{3}H-Thymidine incorporation into MDA PCa 118b cells (118b) and PMOs grown separately or after 48 h of coculture with varying concentrations of dovtinib; **P*<0.05; ***P*<0.001, two-tailed *t* tests. (**D**) Western blot analysis of PCa cells and PMOs treated with increasing concentrations of dovitinib. β-Actin was used as a loading control.

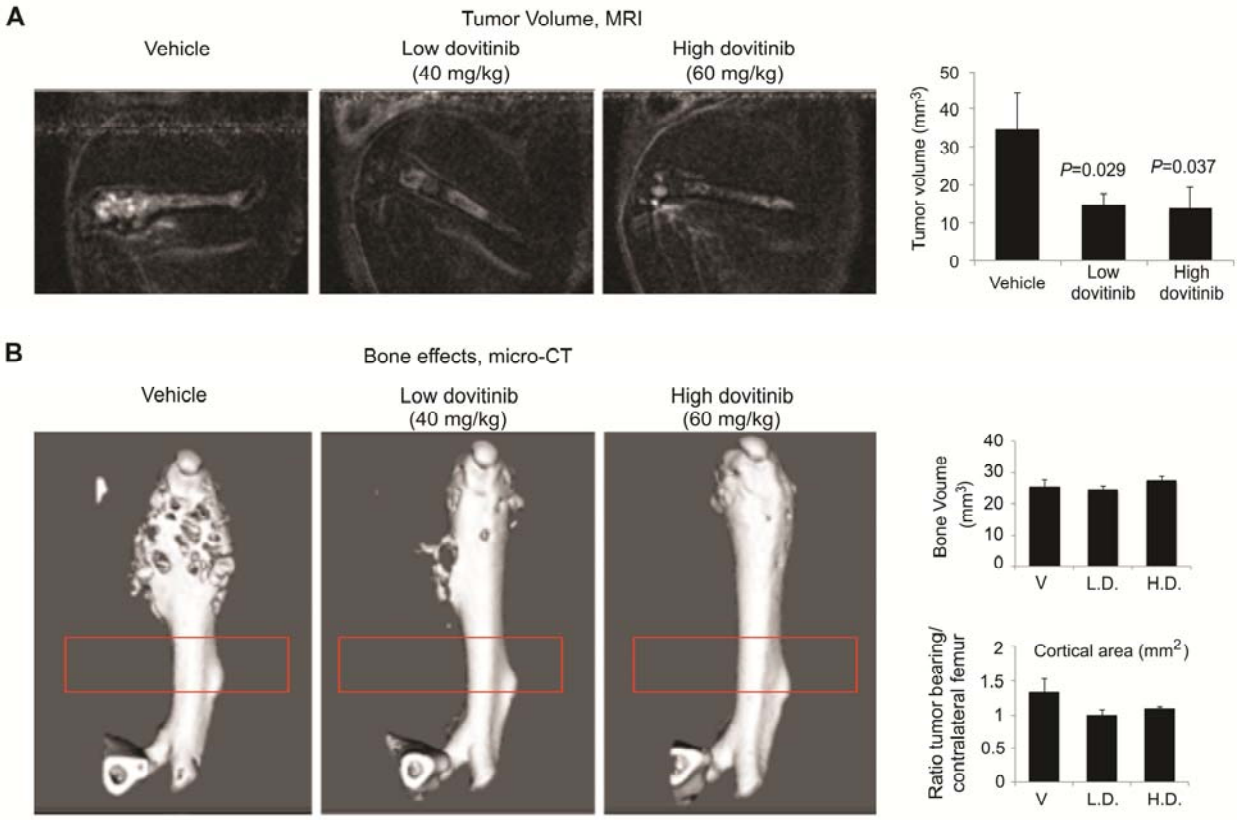


Fig. S2. Effect of 3 weeks of dovitinib treatment on mice bearing MDA PCa 118b cells in the right femurs. (**A**) Left: In vivo MR images show that dovitinib inhibited the growth of MDA PCa 118b tumors. Sagittal MR images of MDA PCa 118b–bearing femurs in control and dovitinib-treated mice were acquired with a T2-weighted fast spin echo sequence with fat suppression. Right: Tumor volumes derived from MR images were significantly smaller in treated mice than in control mice, by one-tailed *t* tests. Error bars indicate standard error of the mean (SEM) (**B**) Left: 3D isosurface micro-CT images of tumor-bearing femurs in control and dovitinib-treated mice. The red outline boxes indicate the area used to calculate relative cortical area (illustrated at right). Right upper panel: bone volume of the femur and patella (including woven bone present in tumor). Right lower panel: relative cortical area of a 3-mm midshaft region of the femur of control and dovitinib-treated mice. Values were calculated as a ratio between tumor-bearing femur and contralateral femur of the same mice. *P*=0.034 by *t*-test comparing cortical area for vehicle vs. two treatment arms pooled together. V, vehicle; L.D. low-dose dovitinib; H.D., high-dose dovitinib. Error bars indicate standard error of the mean (SEM).

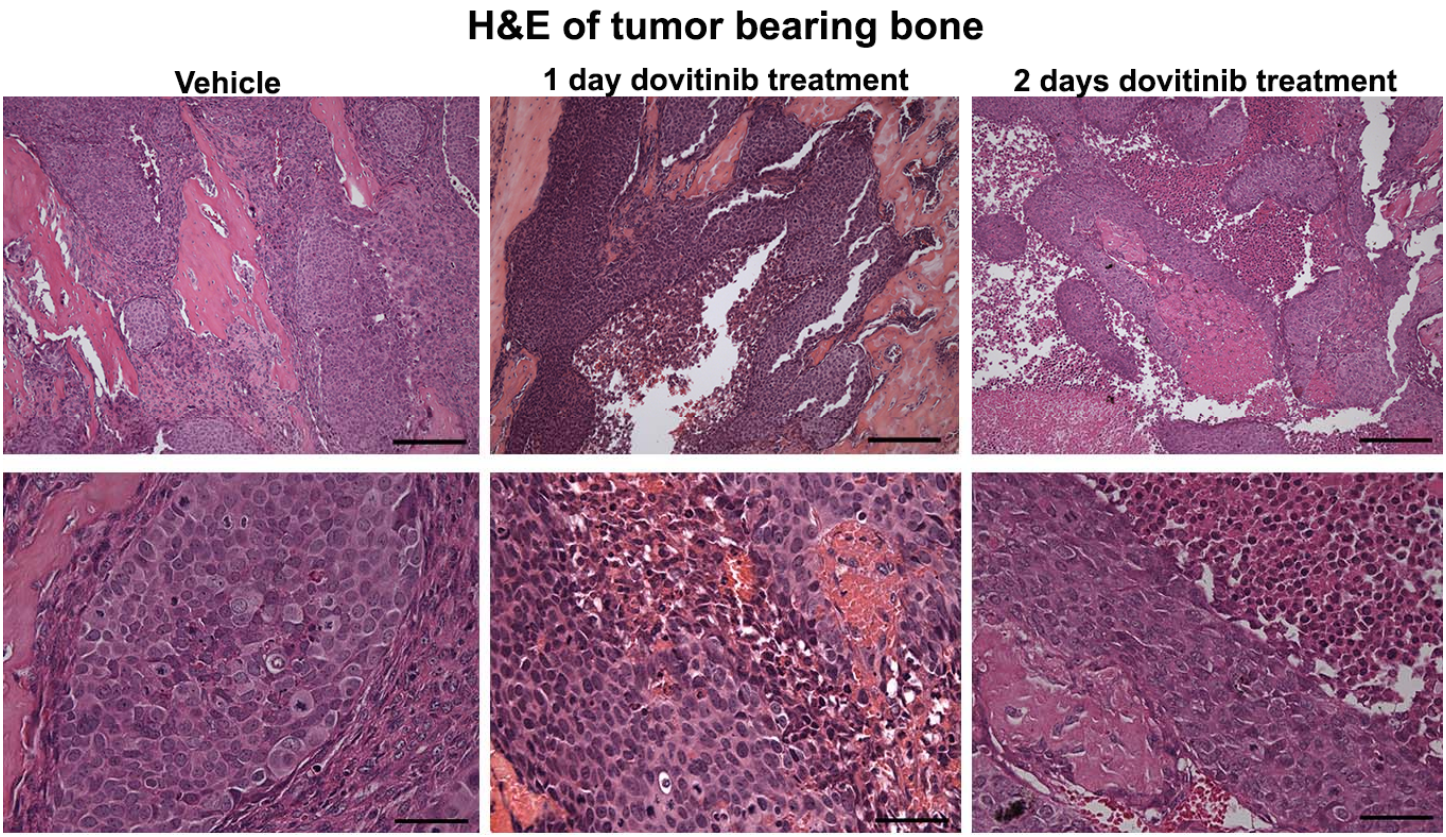


Fig. S3. Effects of 1 day and 2 days of dovitinib treatment on MDA PCa 118b bone tumors. Representative H&E-stained sections of MDA PCa 118b cells grown in femurs of mice treated without dovitinib (vehicle; left) or with dovitinib for 1 day (middle) or 2 days (right). Scale bars, 200 μm (top panels) and 50 μm (lower panels).

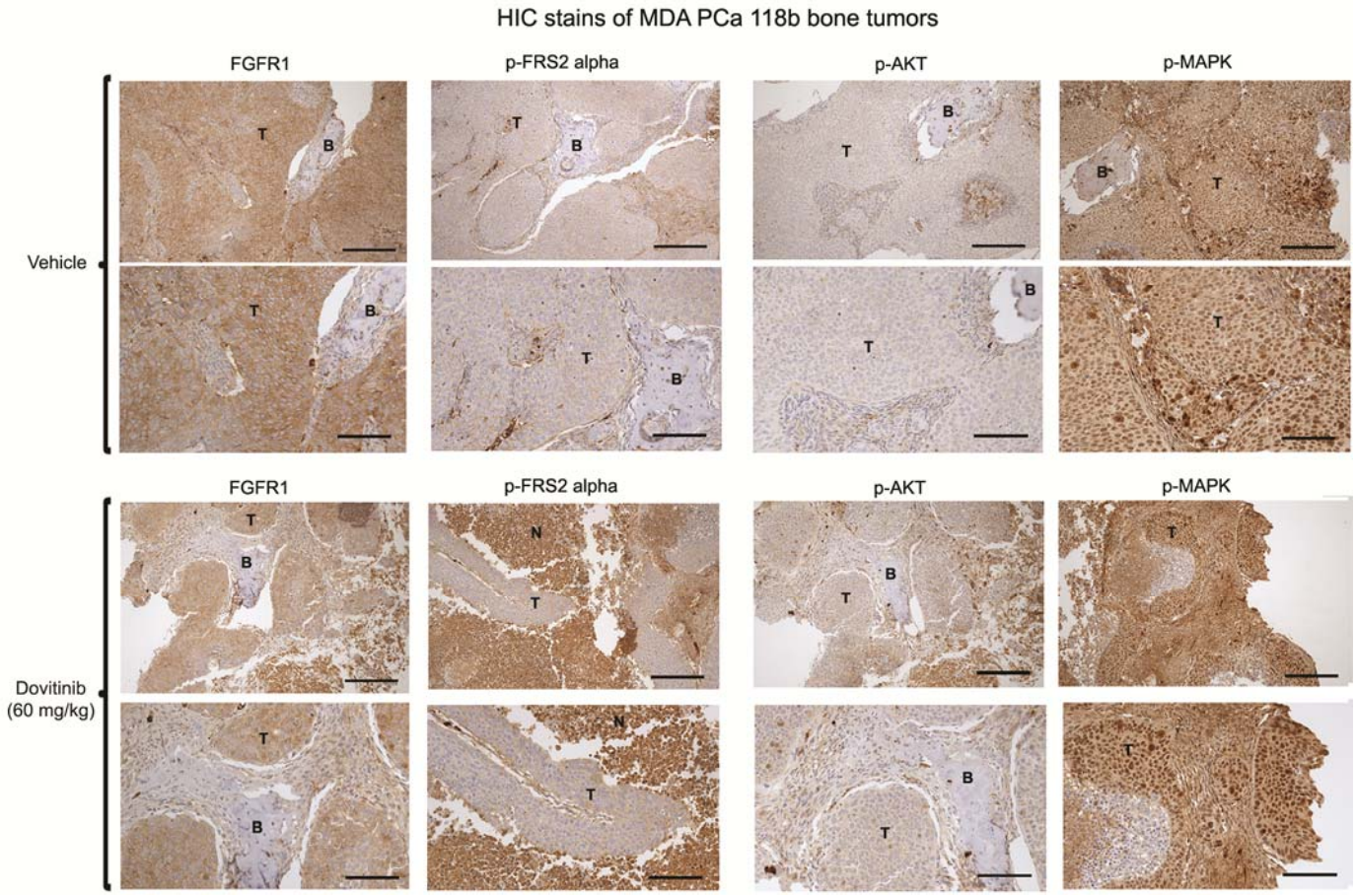
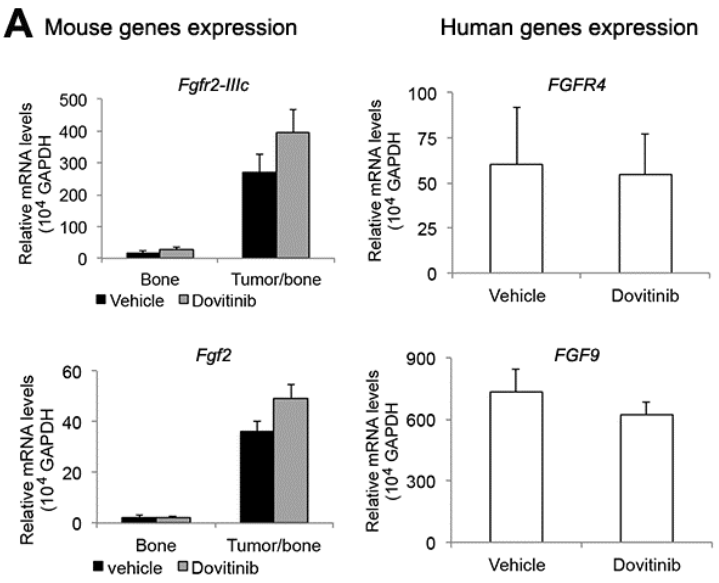


Fig. S4. Effects of 7 days of dovitinib treatment on the expression of FGFR1, p-FRS2-alpha, p-AKT, and p-MAPK on MDA PCa 118b bone tumors. Representative immunohistochemical-stained tissue sections of MDA PCa 118b cells grown in femurs of mice treated without dovitinib (vehicle) or with dovitinib for 7 days. T, tumor; B, bone; N, necrosis. Scale bars, 200 μm (top panels) and 50 μm (lower panels) for each set of treated and control conditions.



B p-MAPK band density on mouse bone

	Band density in Western blot							
	Vehicle				Dovitinib (60mg/kg)			
Mouse	V1	V2	V3	V4	D1	D2	D3	D4
p-MAPK	3282	9268	4393	11871	2957	2987	3002	2984
eIF4E	12705	13297	12882	13198	12079	12124	12105	12307
Ratio p-MAPK/eLF4E	0.2583	0.697	0.3411	0.8994	0.2449	0.2464	0.248	0.2425
Mean	0.55				0.25			
SD	0.3				0.002			
P	0.09							

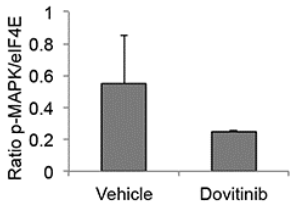


Fig. S5. Expression of *Fgfr2-IIIc* and *Fgf2 RNA*, *FGFR4* and *FGF9* RNA, and p-MAPK and eIF4E protein in mouse femurs with or without MDA PCa 118b. **(A)** Relative RNA expression of mouse *Fgfr2-IIIc* and *Fgf2* and of human *FGFR4* and *FGF9* in mouse femur with MDA PCa 118b tumor (Tumor/bone) and without tumors (Bone) after 7 days of treatment with dovitinib or vehicle. Real time RT-PCR was done with mouse- and human-specific primers. **(B) Top**. Band densities on western blots of contralateral (non-tumorous) femurs of mice with MDA PCa 118b bone tumors treated for 7 days with vehicle or with dovitinib. Lower rows show ratio of band densities. **Bottom.** Graphic illustration of mean values in the table.

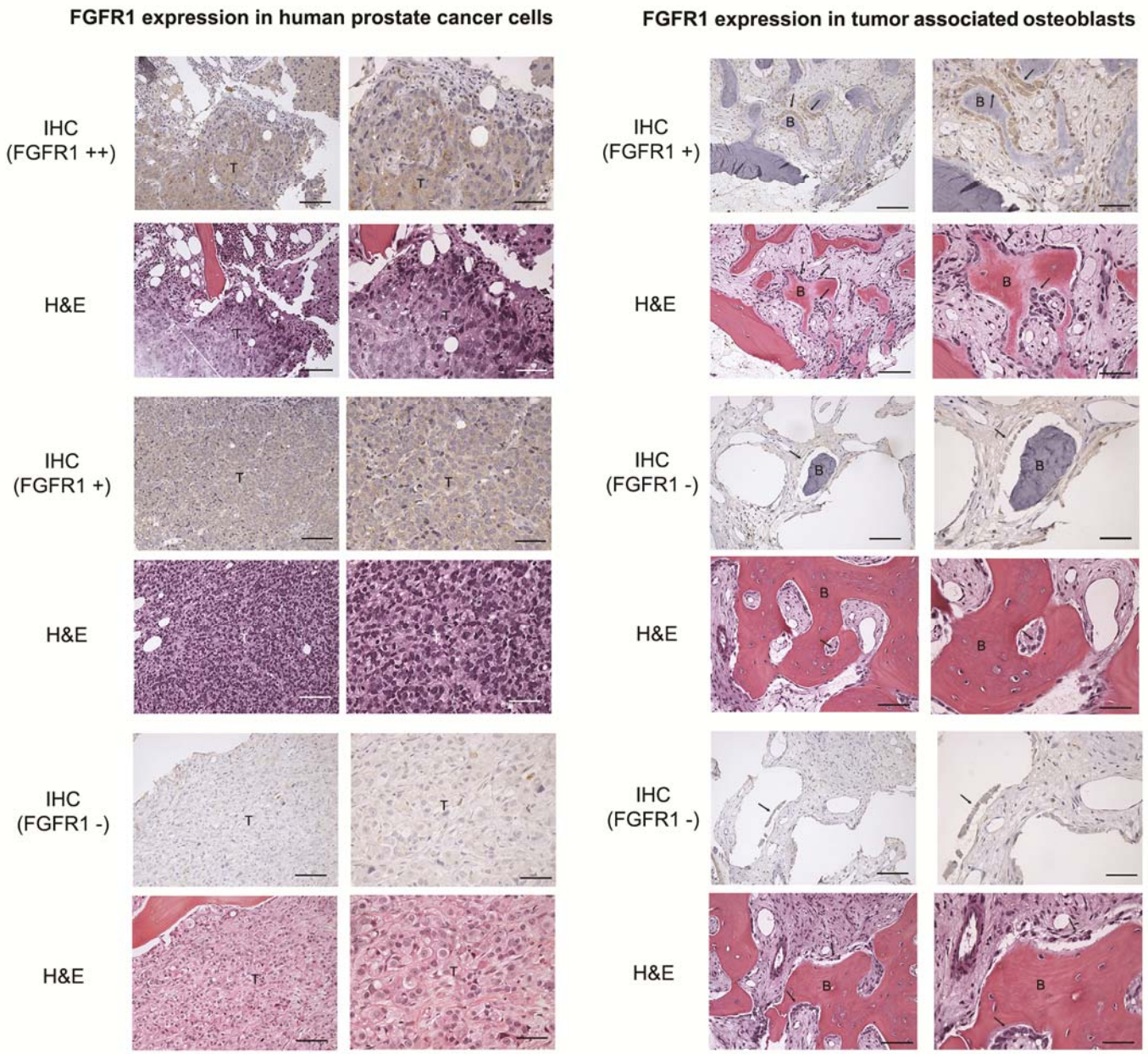


Fig S6. Expression of FGFR1 in PCa cells and in tumor-associated osteoblasts in bone biopsy specimens obtained from men in the dovitinib trial before treatment. Representative photomicrographs are shown for immunohistochemical stains with antibody to FGFR1 (Epitomics) and for H&E. Panels under the subheading 'FGFR1 expression in prostate cancer cells' illustrate "++", "+" and "-" results in PCa cells, as indicated in Table S19. Left panels, scale bar indicates 100 μm; right panels, 50 μm. Panels under 'FGFR1 expression in tumor-associated osteoblasts' illustrate "+" and "-" results, as indicated in Table S19. In cases of "-" results, two different areas containing tumor-associated osteoblasts are shown. Left panels, scale bar indicates 100 μm;

right panels, 50 μm. T, tumor; B, bone; arrows indicate osteoblasts. Note that the bone tissue had detached in many of the histologic slides with immunohistochemical stains.

Table S1. Primer sequences used for RT-PCR

	Primer Name	Exon	Primer Sequence
Human primers	hFGF9-257F	1	GGA AAG ACC ACA GCC GAT TT
	hFGF9-347R	2	AGG TAG AGT CCA CTG TCC ACG
	hFGFR1-894F	7a	CAA GAT TGG CCC AGA CAA CC
	hFGFR1-982R	8	AGT GAA GCA CCT CCA TCT CT
	hFGFR3-419F	3	AGG CTG AGG ACA CAG GTG TG
	hFGFR3-493R	4	CCA GCA GCT TCT TGT CCA TC
	hFGFR4-1358F	10b	ATC TAC CTC TCG ACC CAC TA
	hFGFR4-1456R	11	CCT CTG CAC GTA CTA CCT GG
	hFGFR1-IIIb943F	8	GGA TTA ATA GCT CGG ATG CG
	hFGFR1-IIIb1166R	9	CAT CTT GTA GAC GAT GAC CGA C
	hFGFR10IIIc965F	8	GAT GGA GGT GCT TCA CTT AAG A
	hFGFR1-IIIc1197R	9	CAT CTT GTA GAC GAT GAC CGA C
Mouse primers	mFGF2-249F		TAT GAA GGA AGA TGG ACG GC
	mFGF2-368R		TAC CAA CTG GAG TAT TTC CG
	mFGFR1-894F	7	TAA GAT CGG GCC AGA CAA CT
	mFGFR1-982R	8	GAT GAA GCA CCT CCA TTT CC
	mFGFR2IIIc-1025F	9	GCT TGG CGG GTA ATT CTA TT
	mFGFR2IIIc-1112R	10	GCT GTA ATC TCC TTT TCT CT
	mFGFR3-383F	4	CCT CAG GAG ATG ACG AAG AT
	mFGFR3-475R	5	CCA GCA GTT TCT TAT CCA TT
	mFGFR4-1349F	10	ACC TGC CTC TCG ATC CGC TT
	mFGFR4-1447R	11	CCT CTG CAC GAA CCA CTT GC
	mFGFR1-IIIb943F	11	GAA TTA ATA GCT CGG ATG CG
	mFGFR1-IIIb1103R	12	ATA GAT GAT GAC AGA GCC CAA
	mFGFR1-IIIc965F	11	AAT GGA GGT GCT TCA TCT ACG G
	mFGFR1-IIIc1134R	12	AAT GAT CTC CAG GTA GAG CGG T

Table S2. Quantitative RT-PCR results.

Gene	Primary mouse osteoblasts	PC3 (human prostate cancer cell line)
Fgfr1	481.6 +/- 34.1	Undetectable
FGFR1	Undetectable	86.2 +/- 9.6
Fgfr2 IIIc	485.5 +/- 24.3	Undetectable
FGFR2 IIIc	0.12 +/-0.02	4.6 +/- 0.2
Fgfr3	9.9 +/- 0.6	Undetectable
FGFR3	1.02 +/- 0.2	5.8 +/- 0.3
Fgfr4	3.4 +/- 0.3	Undetectable
FGFR4	Undetectable	145.3 +/- 11.7
Fgf2	382.1 +/- 0.3	Undetectable
FGF2	Undetectable	78.3 +/- 3.8
Fgf9	Undetectable	Undetectable
FGF9	Undetectable	0.41+/- 0.3
Fgfr1-IIIb	0.29+/- 0.29	Undetectable
FGFR1-IIIb	Undetectable	Undetectable
Fgfr1-IIIc	3035.29+/- 170	Undetectable
FGFR1-IIIc	Undetectable	82.5+/- 25

Table S3. Relative mRNA levels of FGF family members in bone with and without tumors. The mRNA levels were normalized to 10^4 *Gapdh* in tumor-bearing bone (tumor/bone) and contralateral bone.

MDA PCa 2b

Sample ID	*Fgf2*		*Fgfr1*		*Fgfr2IIIc*		*Fgfr3*		*Fgfr4*	
	Bone	Tumor/ bone	Bone	Tumor/ bone	Bone	Tumor/ bone	Bone	Tumor/ bone	Bone	Tumor/ bone
	T-mean	T-mean	T-mean	T-mean	T-mean	T-mean	T-mean	T-mean	T-mean	T-mean
Mouse 1	9.28	273.01	30.67	547.72	38.47	238.11	7.52	10.95	153.61	12.50
Mouse 2	6.08	112.00	33.80	431.93	30.14	57.28	3.01	15.52	286.77	16.65
Mouse 3	12.30	163.67	41.31	572.52	47.28	54.50	11.45	28.48	152.01	11.82
Mouse 4	21.79	151.17	93.66	542.94	71.17	62.48	13.88	19.53	152.55	18.47
Mouse 5	22.79	177.17	112.42	400.19	115.58	147.91	6.66	26.03	351.87	36.43
Mouse 6	28.44	114.07	76.03	637.31	104.77	339.74	9.39	29.40	372.48	20.68
Mean	16.78	165.18	64.65	522.10	67.90	150.00	8.65	21.65	244.88	19.43
SE	3.60	24.09	14.03	36.47	14.56	48.01	1.56	3.07	42.80	3.67
P	0.0021		0.0001		0.11		0.006		0.0025	

MDA PCa 118b

Sample ID	*Fgf2*		*Fgfr1*		*Fgfr2IIIc*		*Fgfr3*		*Fgfr4*	
	Bone	Tumor/ bone	Bone	Tumor/ bone	Bone	Tumor/ bone	Bone	Tumor/ bone	Bone	Tumor/ bone
	T-mean	T-mean	T-mean	T-mean	T-mean	T-mean	T-mean	T-mean	T-mean	T-mean
Mouse 7	18.68	152.99	176.58	800.35	330.41	407.29	3.81	7.45	180.55	10.67
Mouse 8	10.77	90.05	67.52	329.19	148.95	395.79	3.34	6.83	186.47	8.02
Mouse 9	47.93	66.04	230.44	788.40	284.72	486.84	6.38	4.50	342.34	27.64
Mouse 10	36.97	92.27	269.84	813.10	218.09	368.29	5.72	6.21	423.95	7.85
Mouse 11	38.31	81.44	202.91	347.03	383.63	320.18	6.75	3.99	383.63	35.04
Mouse 12	24.68	75.51	171.14	805.25	339.57	528.01	3.61	13.02	120.54	10.28
Mean	29.56	93.05	186.40	647.22	284.23	417.73	4.93	7.00	272.91	16.58
SE	5.67	12.62	28.07	97.83	35.47	31.35	0.62	1.32	51.35	4.79
P	0.011		0.0027		0.033		0.30		0.0034	

MDA PCa 183

Sample ID	*Fgf2*		*Fgfr1*		*Fgfr2IIIc*		*Fgfr3*		*Fgfr4*	
	Bone	Tumor/ bone	Bone	Tumor/ bone	Bone	Tumor/ bone	Bone	Tumor/ bone	Bone	Tumor/ bone
	T-mean	T-mean	T-mean	T-mean	T-mean	T-mean	T-mean	T-mean	T-mean	T-mean
Mouse 13	20.39	134.27	59.34	651.68	67.74	366.76	6.63	20.05	217.65	11.41
Mouse 14	21.18	287.62	68.97	879.79	62.59	769.68	4.16	26.09	511.24	8.45
Mouse 15	6.18	419.56	43.50	1127.24	59.79	1267.08	5.29	26.51	456.01	6.51
Mouse 16	14.38	349.56	45.40	1251.47	56.29	1046.63	4.51	35.80	326.55	27.04
Mouse 17	12.15	419.58	43.94	1926.68	69.98	1203.25	8.91	43.19	407.15	21.07
Mean	**14.86**	**322.12**	**52.23**	**1167.37**	**63.28**	**930.68**	**5.90**	**30.33**	**383.72**	**14.90**
SE	2.77	53.02	5.11	216.09	2.51	165.05	0.87	4.08	51.42	3.93
P	0.005		0.007		0.006		0.002		0.002	

T-mean is mean of technical duplicates

Table S4. Relative mouse *Fgfr1-IIIc* mRNA levels. The mRNA levels were normalized to 10^4 Gapdh in MDA PCa 2b tumor-bearing bone (tumor/bone) and contralateral (sham injected) bone.

MDA PCa 2b				
Mouse ID		Test 1	Test 2	T-Mean
Tumor/bone	Mouse 1	1241.37	1695.76	1468.56
	Mouse 2	1103.38	1571.27	1337.32
	Mouse 3	476.96	633.72	555.34
	Mouse 4	774.82	915.05	844.94
	Mouse 5	722.93	842.02	782.48
	Mouse 6	607.91	555.53	581.72
	Mean			928.39
	SE			157.76
Bone	Mouse 7	105.98	184.53	145.26
	Mouse 8	96.85	91.63	94.24
	Mouse 9	68.96	87.90	78.43
	Mouse 10	80.88	138.88	109.88
	Mouse 11	361.47	392.82	377.14
	Mouse 12	241.81	231.96	236.88
	Mean			173.64
	SE			46.78
P				0.0078

Test 1 and Test 2 are technical duplicates, T-mean is mean of technical duplicates

MDA PCa 118b				
Sample ID		Test 1	Test 2	T-mean
Tumor/bone	Mouse 13	1377.38	2206.76	1792.07
	Mouse 14	620.68	853.78	737.23
	Mouse 15	727.96	1001.34	864.65
	Mouse 16	131.39	191.04	161.21
	Mouse 17	1001.34	1406.32	1203.83
	Mouse 18	638.13	612.14	625.14
	Mean			897.35
	SE			226.36
Bone	Mouse 19	40.16	87.90	64.03
	Mouse 20	92.27	100.27	96.27
	Mouse 21	96.18	127.80	111.99
	Mouse 22	74.42	104.53	89.48
	Mouse 23	240.14	149.89	195.01
	Mouse 24	66.15	44.25	55.20
	Mean			102.00
	SE			20.47
P				0.0166

MDA PCa 183				
Mouse ID		Test 1	Test 2	T-mean
Tumor/bone	Mouse 25	497	796	646.50
	Mouse 26	872	1065	968.50
	Mouse 27	824	1182	1003.00
	Mean			872.67
	SE			113.52
Bone	Mouse 28	52	62	57.00
	Mouse 29	30	29	29.50
	Mouse 30	23	48	35.50
	Mean			40.67
	SE			8.35
P				0.0207

Test 1 and Test 2 are technical duplicates, T-mean is mean of technical duplicates

Table S5. Relative mRNA levels of *FGFR-IIIb and FGFR1-IIIc* in MDA PCa 2b tumor-bearing bone. The levels were normalized to 104 Gapdh.

MDA PCa 2b				
Sample ID	*FGFR1-IIIb*		*FGFR1-IIIc*	
	Mean	SD	Mean	SD
M2b-1	0.3	1.14	26	3
M2b-2	0.2	0.01	20	2
M2b-3	0.5	0.14	28	3
MDA PCa 118b				
	FGFR1-IIIb		*FGFR1-IIIc*	
	Mean	SD	Mean	SD
M118b-1	0.6	0.15	75	16
M118b-2	5.5	0.4	240	5
M118b-3	10	1.4	615	110
MDA PCa 183				
	FGFR- IIIb		*FGFR1-IIIc*	
	Mean	SD	Mean	SD
M183-1	0.5	0.1	27	1
M183-2	0.24	0.1	29	4
M183-3	2.4	0.1	244	39
Values are Mean and SD of experimental duplcates.				

Table S6. Expression of *FGFR1* in prostate and prostate cancer tissues, xenografts, and cell lines				
Reads per kilobase per million [RPKM]	**Prostate cancer specimens* (n=136)**	**Benign prostate tissues next to pCa (n=19)**	**Patient-derived xenografts (PDX) (n=17)**	**Prostate cancer cell lines (n=10)**
More than 100	7 (5%)	2 (11%)	1 (6%)	0
50-100	32 (24%)	8 (42%)	2 (12%)	3 (30%)
20-50	63 (46%)	7 (37%)	6 (35%)	2 (20%)
10-20	26 (19%)	2 (10%)	3 (18%)	2 (20%)
Less than 10	8 (6%)	0	5 (29%)	3 (30%)

*From primary tumors and non-bone metastases.

Table S8. Relative *Fgfr1* mRNA levels in MDA PCa 118b tumor-bearing bone. The levels were compared contralateral (sham-injected) bone of mice treated with vehicle or dovitinib and normalized to 10^4 GAPDH

Sample ID		*Fgfr1*				*FGFR1*	
		Bone		Tumor/bone		Tumor/bone	
		T-mean	T-SD	T-mean	T-SD	T-mean	T-SD
Vehicle	Mouse 1	65.05	2.87	1434.83	402.48	932	50.21
	Mouse 2	7.55	0.85	677.06	23.22	809	71.31
	Mouse 3	8.81	2.76	670.47	88.46	1200	47.02
	Mouse 4	4.43	1.14	1150.35	22.55	1314	90.07
	Mean	21.46		983.1775		1063.75	
	SE	14.56		187.84		116.70	
Sample ID		**T-mean**	**T-SD**	**T-mean**	**T-SD**	**T-mean**	**T-SD**
Dovitinib	Mouse 5	28.9	0.99	369.06	61.22	164	23.99
	Mouse 6	17.19	2.9	253.00	39.62	343.00	40.27
	Mouse 7	16.86	1.56	248.66	99.57	345.00	16.88
	Mouse 8	24.05	0.71	418.82	77.56	583.00	17.15
	Mean	21.75		322.385		358.75	
	SE	2.90		42.55		171.90	
P				0.0139		0.0028	

T-mean and T-SD are means and SD of technical duplicates

Table S9. Growth plate and growth-plate-to-tumor distance in MDA PCa 118b tumor-bearing bone. The distances were compared to contralateral (sham-injected) bone of mice treated with vehicle or dovitinib

Mouse ID		Growth plate width (μm)		Growth plate to tumor boundary distance (μm)[1]
		Tumor/bone	**Bone**	**Tumor/bone**
Vehicle	Mouse 1	107.875493	104.404961	194.28251
	Mouse 2	103.587525	108.508409	2294.0817
	Mouse 3	106.974765	105.089783	559.107768
	Mouse 4	93.405455	121.570045	59.767309
	Mouse 5	123.698569	117.252708	132.167605
	Mouse 6	115.464942	121.196652	224.945946
	Mouse 7	119.422147	110.636258	614.638238
	Mouse 8	127.151142	114.628284	641.153296
	Mean	112.20	112.91	590.02
	SE	3.99	2.40	256.65
Dovitinib		Tumor/bone	Bone	Tumor/bone
	Mouse 9	126.956761	192.71832	484.822467
	Mouse 10	243.152194	190.218118	910.068076
	Mouse 11	248.679139	183.143405	145.21193
	Mouse 12	230.4684	184.339013	771.537902
	Mouse 13	335.837736	311.25522	810.466255
	Mouse 14	466.897715	348.303455	1435.080923
	Mouse 15	380.068954	306.727494	668.129205
	Mouse 16	391.117844	303.917094	425.374364
	Mean	302.90	252.58	706.34
	SE	38.83	25.04	135.75

[1]Values are the average distance between the growth plate of the femoral distal metaphysis and the tumor boundary. Distance to the tumor front boundary was measured approximately every 50 μm along the entire growth plate.

Table S10. Serum FGF23 levels in MDA PCa 118b tumor-bearing mice treated with vehicle or dovitinib							
Vehicle				Dovitinib			
Sample ID	**Test 1**	**Test 2**	**T-mean**	**Sample ID**	**Test 1**	**Test 2**	**T-mean**
Mouse 1	0.91	1.55	1.23	Mouse 9	1.62	1.04	1.33
Mouse 2	0	0.27	0.135	Mouse 10	0.85	0.52	0.685
Mouse 3	0.14	0.39	0.265	Mouse 11	0.78	0.52	0.65
Mouse 4	0	0	0	Mouse 12	0.78	0.59	0.685
Mouse 5	0.33	0	0.165	Mouse 13	1.17	1.1	1.135
Mouse 6	0	0	0	Mouse 14	2.46	2.07	2.265
Mouse 7	1.17	0	0.585	Mouse 15	1.43	1.36	1.395
Mouse 8	0.27	0	0.135				
Mean			0.31				1.16
SE			0.41				0.58
P							0.0058
Test 1 and Test 2 are technical duplicates. T-mean is the mean of technical duplicates							

Table S11. Band intensities on western blots of mouse femurs							
Vehicle				**Dovitinib**			
Sample ID	**p-FRS2-α**	**T-FRS2-α**	**Ratio p-FRS2-α/T-FRS2-α**	**Sample ID**	**p-FRS2-α**	**T-FRS2-α**	**Ratio p-FRS2-α/T-FRS2-α**
Mouse 1	3772.56	5758.15	0.66	Mouse 5	861.52	9325.78	0.09
Mouse 2	4521.69	8364.78	0.54	Mouse 6	1190.47	7593.76	0.16
Mouse 3	4126.69	5801.05	0.71	Mouse 7	575.74	9360.24	0.06
Mouse 4	4186.03	7416.29	0.56	Mouse 8	765.92	14119.78	0.05
Mean			0.62				0.09
SD			0.08				0.05

Table S12. Bone histomorphometric analysis of contralateral (non-tumorous) femurs of mice with MDA PCa 118b bone tumors

Vehicle			Dovitinib		
Sample ID	**BS/BV (mm^{-1})**	**Tb.Th (μm)**	**Sample ID**	**BS/BV (mm^{-1})**	**Tb.Th (μm)**
Mouse 1	64.04	31.23	Mouse 9	58.75	34.04
Mouse 2	34.30	58.31	Mouse 10	28.26	70.78
Mouse 3	67.97	29.42	Mouse 11	60.99	32.79
Mouse 4	70.65	28.31	Mouse 12	43.26	46.23
Mouse 5	60.22	33.21	Mouse 13	42.62	46.93
Mouse 6	72.26	27.67	Mouse 14	28.20	70.92
Mouse 7	55.02	36.35	Mouse 15	46.99	42.56
Mouse 8	66.94	29.87	Mouse 16	47.47	42.13
Mean	61.42	34.30	Mean	44.57	48.30
			T-Test	0.015	0.044

Table S13. Micro-CT analysis of femurs of mice treated with vehicle or dovitinib for 4 weeks

Vehicle			Dovitinib		
Sample ID	**TRI-BS/BV**	**TRI-Tb.Th**	**Sample ID**	**TRI-BS/BV**	**TRI-Tb.Th**
Mouse 1	44.20	0.0453	Mouse 9	31.28	0.063
Mouse 2	33.02	0.0606	Mouse 10	30.06	0.066
Mouse 3	42.93	0.0466	Mouse 11	38.39	0.052
Mouse 4	46.18	0.0433	Mouse 12	38.52	0.051
Mouse 5	50.38	0.0397	Mouse 13	42.23	0.047
Mouse 6	50.22	0.0398	Mouse 14	43.31	0.046
Mouse 7	45.96	0.0435	Mouse 15	33.70	0.059
Mouse 8	45.18	0.0443	Mouse 16	38.61	0.051
Mean	44.76	0.045		37.013	0.055
SE	5.43	0.0067		4.87	0.0075
P				0.0095	0.018

Table S14. Tumor volume of MDA PCa 118b tumor-bearing mice assessed by MRI. Tumor volume was determined by fat-suppressed T2-weigthed fast-spin echo MRI after 7 days of dovitinib treatment.

Vehicle		Low dovitinib dose (40 mg/kg)		High dovitinib dose (60 mg/kg)	
Sample ID	Tumor Volume (mm^3)	Sample ID	Tumor Volume (mm^3)	Sample ID	Tumor Volume (mm^3)
Mouse 1	8.40	Mouse 13	9.79	Mouse 26	64.64
Mouse 2	40.84	Mouse 14	26.07	Mouse 27	1.57
Mouse 3	53.06	Mouse 15	26.83	Mouse 28	17.67
Mouse 4	15.83	Mouse 16	13.42	Mouse 29	3.39
Mouse 5	8.19	Mouse 17	5.44	Mouse 30	4.88
Mouse 6	16.87	Mouse 18	15.51	Mouse 31	3.78
Mouse 7	80.26	Mouse 19	14.36	Mouse 32	4.51
Mouse 8	36.25	Mouse 20	5.32	Mouse 33	0.69
Mouse 9	22.14	Mouse 21	1.16	Mouse 34	16.88
Mouse 10	77.13	Mouse 22	3.26	Mouse 35	6.40
mouse 11	28.95	Mouse 23	0.00	Mouse 36	4.40
Mouse 12	251.73	Mouse 24	77.88	Mouse 37	17.37
		Mouse 25	19.03		
Mean	53.30	Mean	16.78	Mean	12.18
SE	19.36	SE	5.64	SE	5.10
P			0.037		0.026
P (comparing vehicle and two treatment groups pooled together)					0.010

Table S15. MDA PCa 118b tumor-bearing mice assessed by dynamic contrast-enhanced MRI after 7 days of dovitinib.

Vehicle		Low dovitinib dose (40 mg/kg)		High dovitinib dose (60 mg/kg)	
Sample ID	Tumor Enhancement	Sample ID	Tumor Enhancement	Sample ID	Tumor Enhancement
Mouse 1	7.108	Mouse 7	2.484	Mouse 13	1.934
Mouse 2	8.135	Mouse 8	2.929	Mouse 14	2.820
Mouse 3	8.798	Mouse 9	6.387	Mouse 15	5.557
Mouse 4	11.232	Mouse 10	4.256	Mouse 16	5.403
Mouse 5	7.269	mouse 11	2.989	Mouse 17	3.002
Mouse 6	10.164	Mouse 12	1.598	Mouse 18	2.030
Mean	8.784	Mean	3.440	Mean	3.458
SE	0.67	SE	0.69	SE	0.66
P			0.0002		0.00021

Table S16. Tumor volumes in tumor-bearing mice assessed by T2-weighted fast spin echo MRI after 3 weeks of dovitinib.

MDA PCa 118b				MDA PCa 183			
Vehicle		Dovitinib		Vehicle		Dovitinib	
Sample ID	Tumor Volume (mm^3)	Sample ID	Tumor Volume (mm^3)	Sample ID	Tumor Volume (mm^3)	Sample ID	Tumor Volume (mm^3)
Mouse 1	43.95	Mouse 9	8.89	Mouse 1	10.74	Mouse 9	2.10
Mouse 2	51.93	Mouse 10	1.42	Mouse 2	4.35	Mouse 10	6.57
Mouse 3	86.08	Mouse 11	23.93	Mouse 3	8.08	Mouse 11	6.57
Mouse 4	58.45	Mouse 12	11.23	Mouse 4	1.83	Mouse 12	6.40
Mouse 5	21.46	Mouse 13	12.87	Mouse 5	4.00	Mouse 13	2.83
Mouse 6	93.36	Mouse 14	6.54	Mouse 6	1.44	Mouse 14	6.84
Mouse 7	45.63	Mouse 15	10.47	Mouse 7	34.35	Mouse 15	28.86
Mouse 8	26.12	Mouse 16	8.57	Mouse 8	6.52	Mouse 16	7.69
Mean	53.37		10.49	Mean	8.91		8.48
SE	9.07		2.28	SD	3.8		2.99
P			0.0004	P			0.93

Table S17. Characteristics of the 34 men enrolled in the dovitinib clinical trial		
Characteristic	**Median (range)**	***n* (%)**
Age, years	68 (57–78)	
Race		
Caucasian		28 (82)
African American		4 (12)
Hispanic		2 (6)
Eastern Cooperative Oncology Group performance status score		
0		11 (32)
1		20 (59)
2		3 (9)
Prior cytotoxic chemotherapy regimens		
0		8 (25)
1		12 (35)
2		7 (20)
3		7 (20)
Prostate-specific antigen concentration, ng/mL	140.3 (7.4-3,229.8)	
Bone-specific alkaline phosphatase concentration, µg/L	54 (13–416)	
Extent of bone metastases		
<10		7 (20)
≧10 to <20		6 (18)
>20		21 (62)
Visceral metastases		
None		19 (56)
Lymph nodes		14 (41)
Liver		4 (12)

Table S18. Toxicity events among 34 men enrolled in the dovitinib clinical trial

Event	Grade 1	Grade 2	Grade 3	Grade 4	Number of patients	% of patients
Fatigue	9	13	3	0	25	74
Diarrhea	18	6	0	0	24	71
Nausea	11	5	1	0	17	50
Anorexia	6	6	0	0	12	35
Rash	6	5	1	0	12	35
Vomiting	10	2	0	0	12	35
Weakness	1	6	3	0	9	26
Anemia	1	6	1	0	8	24
Elevated gamma-glutamyltransferase	3	2	2	0	7	21
Elevated alkaline phosphatase	1	2	2	0	5	15
Thromboembolism	0	1	1	0	2	6
Hypertension	0	0	1	0	1	3

Table S19. Findings from immunohistochemical analyses of bone biopsies obtained from men in the dovitinib trial at baseline and after 8 weeks of treatment

Patient ID	Time of biopsy	Prostate Cancer				Tumor-associated osteoblasts			
		FGFR1	p-MAPK	p-S6K	p-FRS2	FGFR1	p-MAPK	p-S6K	p-FRS2
1	Bsl	++	+++	+++	ND	+	+	+	ND
	8 weeks	-	++	+++		onp	onp	onp	
2	Bsl	+	+++	+++	ND	few +	-	few +	ND
	8 weeks	-	+++	+++		-	-	few +	
3	Bsl	+	+++	+++	ND	onp	onp	onp	ND
	8 weeks	-	+++	+++		weak +	+	few +	
4	Bsl	-	+++	ND	+/++	+	onp	ND	-
	8 weeks	-	+++		++	onp	onp		onp
5	Bsl	-	+/+++	ND	+	+	onp	ND	onp
	8 weeks	-	+++		-	onp	-		-
6	Bsl	-	+++	-	ND	onp	onp	onp	ND
	8 weeks	-	+/+++	++		weak +	focal +	+	
7	Bsl	-	+++	-	ND	-	onp	-	ND
	8 weeks	+	+++	++		onp	onp	onp	
In the cases below, tissues derived from bone biopsy after 8 weeks of treatment did not contain PCa cells and thus were not evaluated									
8	Bsl	+	-	-	ND	onp	onp	onp	ND
9	Bsl	-	+++	ND	0	+	-	ND	-
10	Bsl	-	+++	ND	+	-	-	ND	-
11	Bsl	-	+	ND	+/++	+	onp	ND	-
12	Bsl	-	+++	-	ND	-	-	weak +	ND
13	Bsl	-	+++	+++	ND	-	+	few +	ND
14	Bsl	-	+++	+++	ND	-	weak +	+	ND
15	Bsl	-	+++	+++	ND	onp	onp	onp	ND
16	Bsl	-	+++	+++	ND	onp	onp	onp	ND

Bsl, baseline; ND, not determined; onp, osteoblasts not present for evaluation