Neuropilin 1 may be Prognostic and Identify a Subgroup of Patients with Metastatic Colorectal Cancer who Benefit from from Tivozanib + mFOLFOX6 Compared to Bevacizumab + mFOLFOX6

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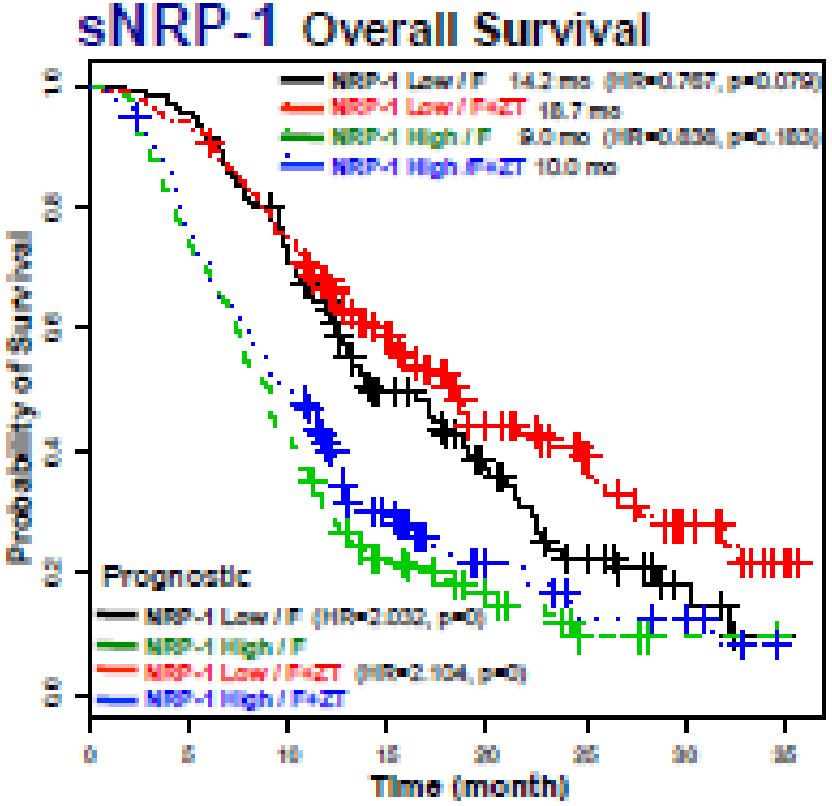
Background

- Tivozanib is a Selective, Potent VEGF-R TKI
  - 8 fold selectivity relative to any other RTK (cKit)
  - $T_{1/2}$ 4.5 days
- BATON-CRC (Biomarker Assessment of Tivozanib in Oncology-colorectal cancer) was a randomized, open-label, phase 2 trial of tivozanib + mFOLFOX6 vs bevacizumab + mFOLFOX6 in patients with previously untreated metastatic CRC (mCRC)
- Neuropilin-1 (NRP-1)
  - When bound, NRP-1 is a VEGFR-2 co-receptor
  - Regulates VEGFR-2 mediated angiogenesis
  - Soluble form binds VEGFa (165)

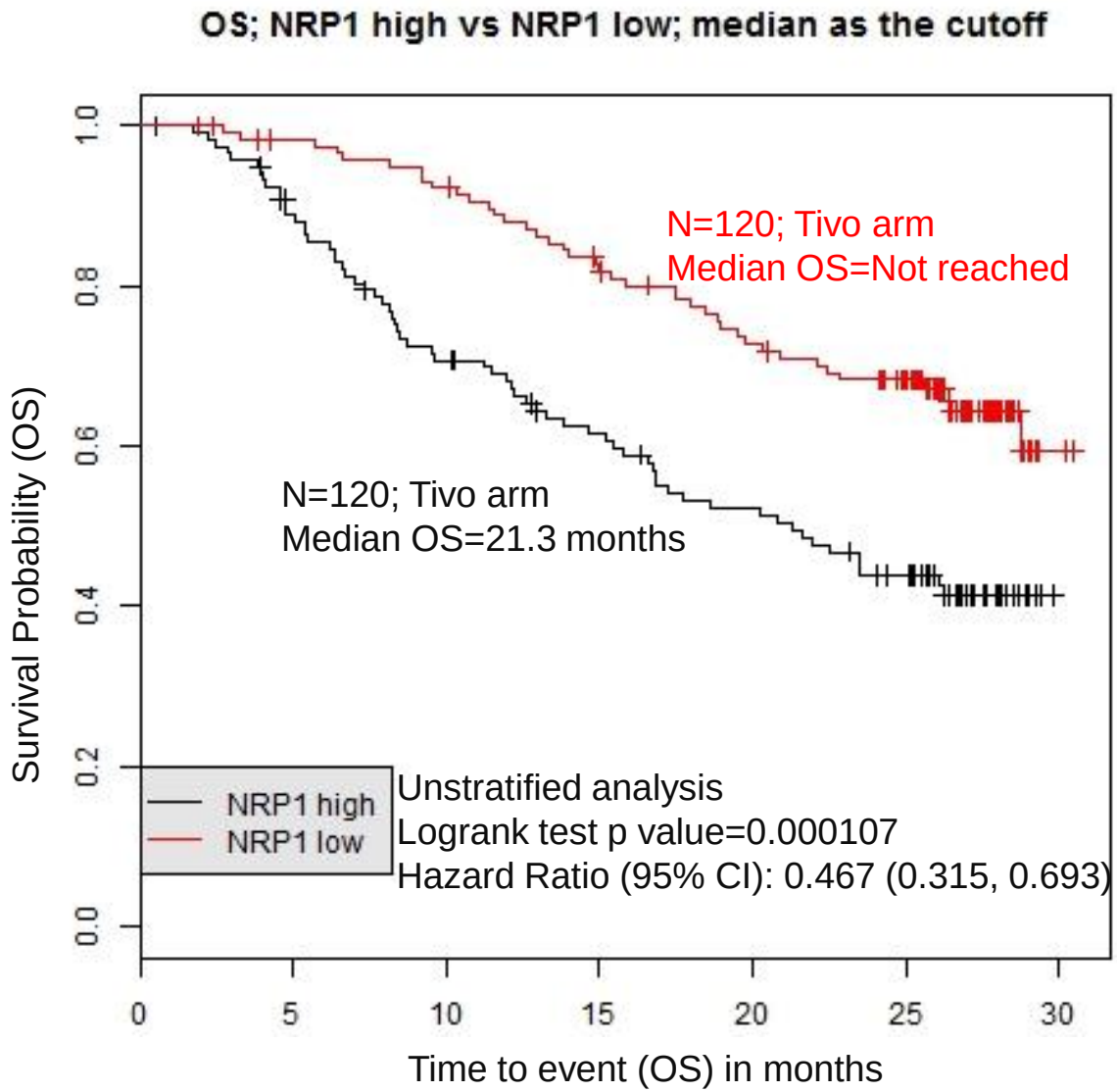
Neuropilin-1 has Prognostic Value in Velour Trial of mCRC



OS: Patients with low plasma NRP-1 (neuropilin 1) may do better in VELOUR (red vs blue & black vs green)

- Prognostic effect High NRP-1: HR=2.104 in ZT, 2.032 in control
- Median: 160 ng/ml (min, max: 34, 387 ng/ml)

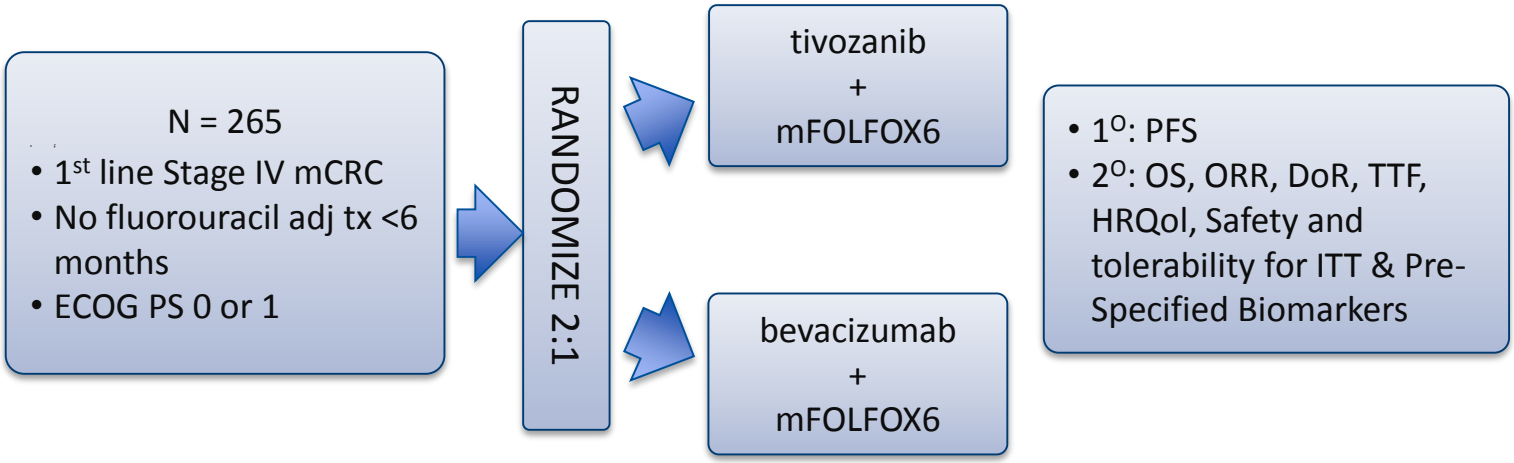
Serum NRP-1 Has Prognostic Value in Renal Cell Cancer



Methods

- Eligible patients
  - No prior systemic chemotherapy, no fluorouracil-containing adjuvant therapy in the previous 6 months, and an ECOG PS ≤1
  - No prior VEGF therapy
- End points
  - Primary end point was progression-free survival (PFS) by investigator radiologic assessment
  - Secondary end points
    - Biomarker subgroup analysis of lactate dehydrogenase (LDH); VEGF A, C, D; CD68; myeloid-derived gene signature; NRP-1; and serum soluble cytokines
- Biomarker analysis
  - Performed using ELISA
  - 164 of 265 patients had samples submitted at time of study closure and initial analysis

Study Design of BATON-CRC



VEGF inhibitor

Tivozanib 1.5 mg once daily for 21 days followed by 7 days off treatment
or
Bevacizumab 5 mg/kg every 2 weeks on days 1 and 15

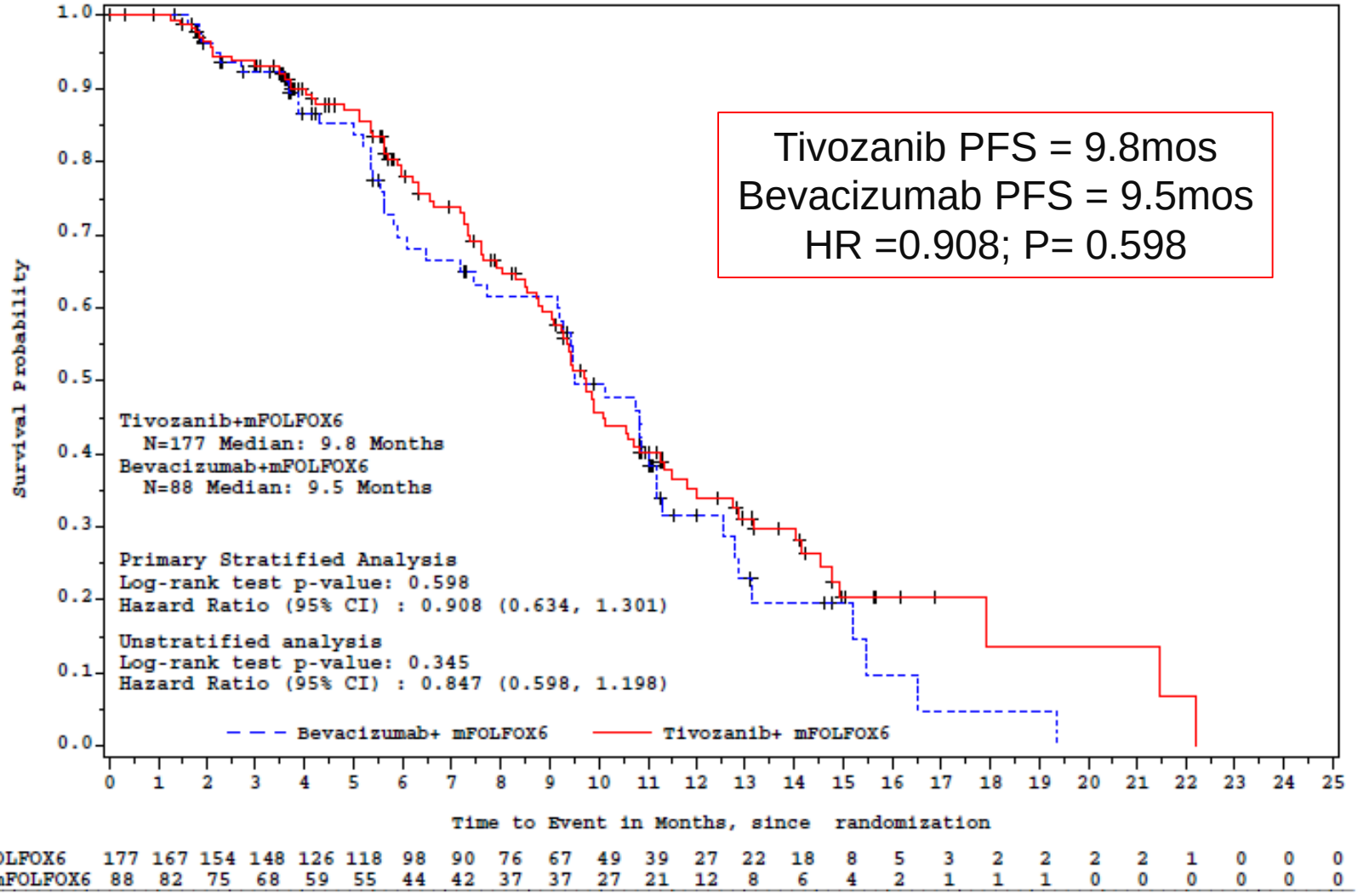
All patients received mFOLFOX6 every 2 weeks of each 28-day cycle

Oxaliplatin: Days 1 and 15: 85 mg/m^2 IV bolus in 500 mL of D5W over 2 hours
Leucovorin Calcium: Days 1 and 15: 400 mg/m^2 IV bolus in 500 mL of D5W over 2 hours
Fluorouracil Bolus: Days 1 and 15: 400 mg/m^2 IV bolus over 5-15 minutes
Fluorouracil Infusion: Days 1-3 and 15-17: 2400 mg/m^{2}continuous IV infusion via infusion pump

Adverse Event Profiles were comparable

	Tivozanib +mFOLFOX6 **(n=177)**		Bevacizumab +mFOLFOX6 **(n=88)**	
Adverse Event, n (%)	**All-Grade**	**Grade 3/4**	**All-Grade**	**Grade 3/4**
Diarrhea	103 (58.2)	19 (10.7)	50 (57.5)	9 (10.3)
Nausea	99 (55.9)	5 (2.8)	47 (54.0)	2 (2.3)
Fatigue	97 (54.8)	20 (11.3)	46 (52.9)	8 (9.2)
Neutropenia	95 (53.7)	70 (39.5)	37 (42.5)	21 (24.1)
Hypertension	79 (44.6)	29 (16.4)	25 (28.7)	9 (10.3)
Peripheral neuropathy	75 (42.4)	18 (10.2)	34 (39.1)	11 (12.6)
Decreased appetite	64 (36.2)	2 (1.1)	25 (28.7)	2 (2.3)
Vomiting	60 (33.9)	10 (5.6)	24 (27.6)	1 (1.1)
Thrombocytopenia	54 (30.5)	10 (5.6)	13 (14.9)	2 (2.3)
Constipation	50 (28.2)	1 (0.6)	32 (36.8)	1 (1.1)
Paresthesia	46 (26.0)	2 (1.1)	20 (23.0)	3 (3.4)
Abdominal pain	45 (25.4)	7 (4.0)	17 (19.5)	5 (5.7)
Dysphonia	42 (23.7)	1 (0.6)	13 (14.9)	0
Mucosal inflammation	40 (22.6)	5 (2.8)	29 (33.3)	6 (6.9)
Asthenia	39 (22.0)	5 (2.8)	17 (19.5)	1 (1.1)
Stomatitis	37 (20.9)	5 (2.8)	14 (16.1)	2 (2.3)
Epistaxis	34 (19.2)	0	25 (28.7)	0
Dyseguesia	26 (14.7)	0	18 (20.7)	0

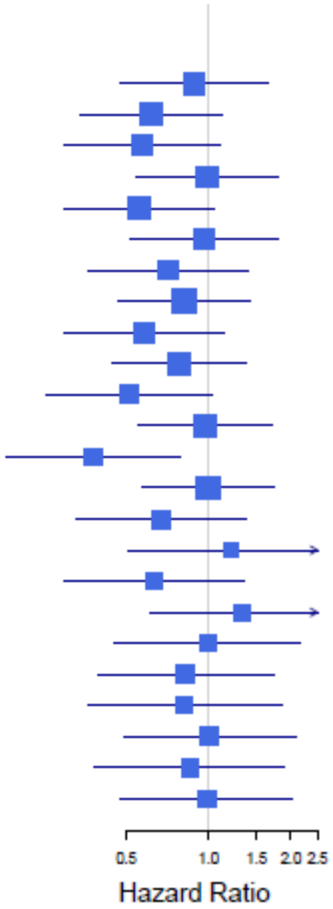
Progression Free Survival (ITT)



Tivozanib PFS = 9.8mos
Bevacizumab PFS = 9.5mos
HR =0.908; P= 0.598

ONLY NRP-1 Demonstrated Predictive Value

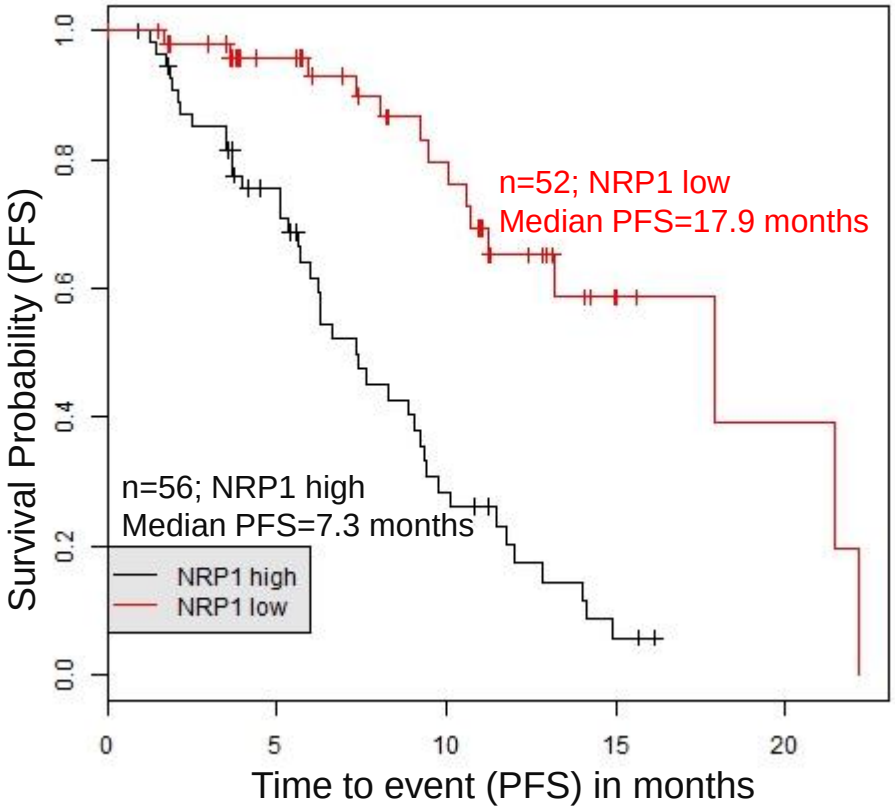
Subgroups	Tivozanib Event/N	Bevacizumab Event/N	HR[95%CI]
Serum VEGF−A < Median	27/54	16/27	0.88 [0.47,1.65]
Serum VEGF−A >= Median	29/54	18/27	0.62 [0.34,1.12]
Serum VEGF−C < Median	23/52	16/26	0.57 [0.3,1.1]
Serum VEGF−C >= Median	33/56	18/28	0.99 [0.55,1.81]
Serum VEGF−C/A < Median	31/56	15/25	0.56 [0.3,1.05]
Serum VEGF−C/A >= Median	25/52	19/29	0.96 [0.52,1.79]
Serum sVEGFR−2 < Median	23/53	14/28	0.71 [0.36,1.4]
Serum sVEGFR−2 >= Median	33/55	20/26	0.81 [0.46,1.43]
Serum sVEGFR−3 < Median	20/51	16/30	0.58 [0.3,1.14]
Serum sVEGFR−3 >= Median	36/57	18/24	0.78 [0.44,1.38]
Serum IL−8 < Median	22/53	14/26	0.52 [0.26,1.04]
Serum IL−8 >= Median	34/55	20/28	0.97 [0.55,1.71]
Serum Neuropilin < Median	15/52	16/28	0.38 [0.18,0.79]
Serum Neuropilin >= Median	41/56	18/26	1 [0.58,1.75]
Tumor VEGF−A < Median	18/38	13/18	0.67 [0.33,1.37]
Tumor VEGF−A >= Median	24/37	7/16	1.21 [0.51,2.87]
Tumor VEGF−C < Median	20/39	11/16	0.63 [0.3,1.34]
Tumor VEGF−C >= Median	22/36	9/18	1.33 [0.61,2.9]
Tumor VEGF−C/A < Median	22/37	9/15	0.99 [0.45,2.18]
Tumor VEGF−C/A >= Median	20/38	11/19	0.83 [0.39,1.73]
Tumor VEGF−D < Median	23/41	8/13	0.82 [0.36,1.85]
Tumor VEGF−D >= Median	19/34	12/21	1.01 [0.49,2.09]
Tumor PIGF < Median	20/38	9/16	0.85 [0.38,1.89]
Tumor PIGF >= Median	22/37	11/18	0.98 [0.47,2.04]



[a]Serum values indicate protein levels in circulation; for tumor biomarkers, the categories indicate RNA expression.
IL-8, interleukin-8; PIGF, placental growth factor; sVEGFR, serum vascular endothelial growth factor receptor; VEGF, vascular endothelial growth factor.

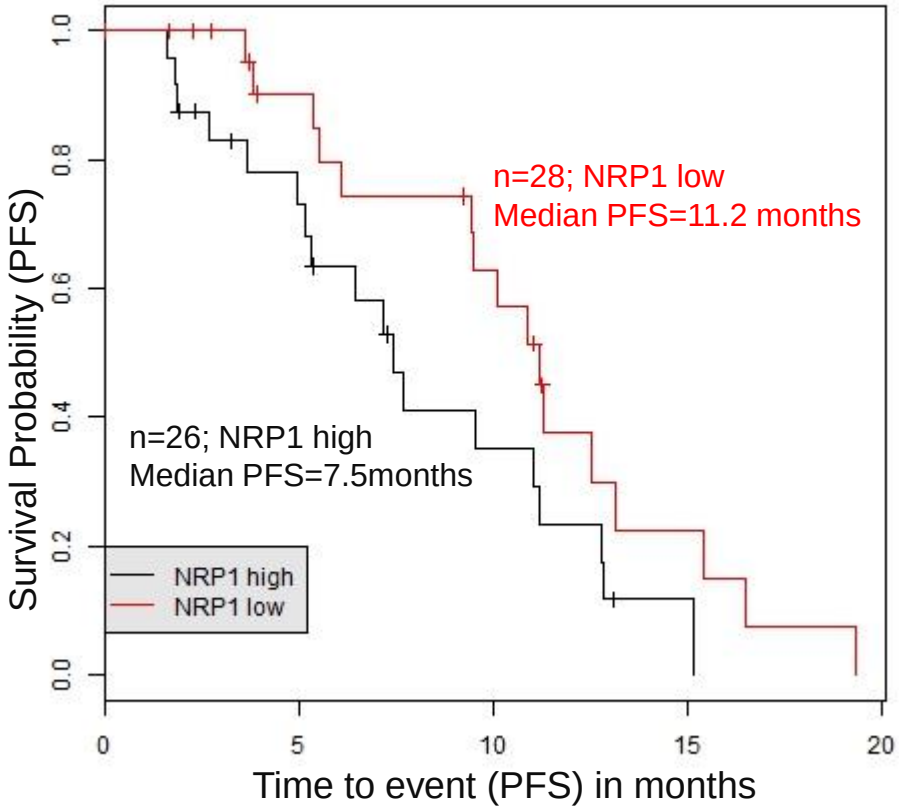
In Both Arms Patients with Low NRP-1 do Better than those with High NRP-1 Using the Median as the Cutoff

(A) PFS for tivozanib arm



Unstratified PFS analysis: N=108; events=56
Logrank test p value=2.88e-7
Hazard Ratio (95% CI): 0.21 (0.11, 0.41)

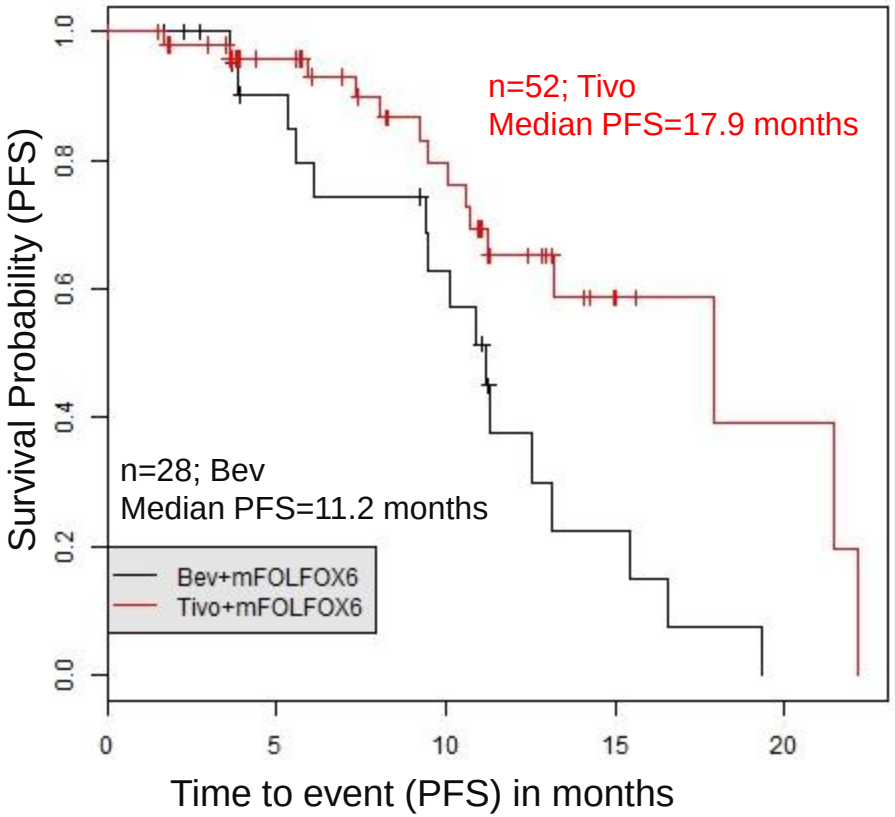
(B) PFS for bevacizumab arm



Unstratified PFS analysis: N=54; events=34
Logrank test p value=0.059
Hazard Ratio (95% CI): 0.506 (0.246, 1.04)

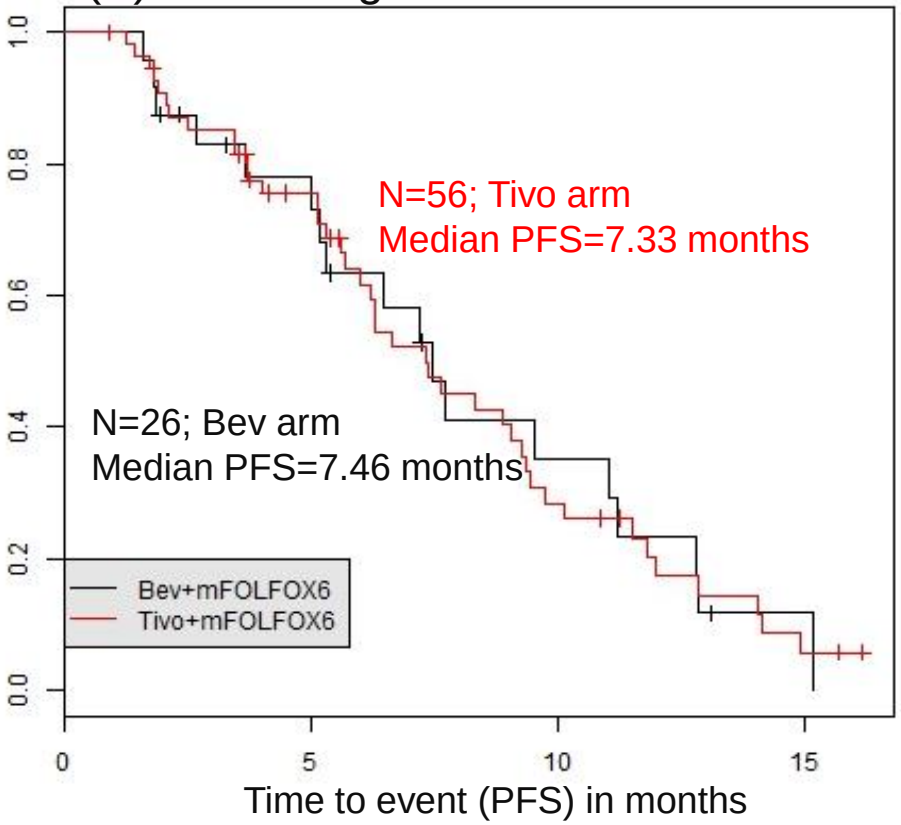
Patients with Low NRP-1 Benefit from Treatment with Tivozanib

(A) NRP-1 low



Unstratified PFS analysis: N=80; events=31
Logrank test p value=0.0075
Hazard Ratio (95% CI): 0.38 (0.183, 0.794)
Multivariate analysis (cancer origin, met sites, LDH)
Wald test p value=0.0034
Hazard Ratio (95% CI): 0.30 (0.133, 0.671)

(B) NRP-1 high



Unstratified PFS analysis: N=82; events=59
Logrank test p value=0.99
Hazard Ratio (95% CI): 1.00 (0.997, 0.575)
Multivariate analysis (cancer origin, met sites, LDH)
Wald test p value=0.68
Hazard Ratio (95% CI): 1.12 (0.639, 1.980)

Using a Second Detection Antibody Results in Qualitatively Similar Data Albeit with having to move the cutpoint

Population:	All LO NRP (Tivo vs Bev)			
Cutoff:30%	Cutoff Value: 382 ng/mL			
	# Subjects	Median Survival		
Tivo	31	17.9		HR: 0.345 (p= 0.034)
Bev	17	10.1		
Cutoff:40%	Cutoff Value: 399 ng/mL			
	# Subjects	Median Survival		
Tivo	40	17.9		HR: .404 (p= 0.027)
Bev	25	11.3		
Cutoff:50%	Cutoff Value: 436 ng/mL			
	# Subjects	Median Survival		
Tivo	53	14.1		HR: 0.529 (p= 0.064)
Bev	26	12.1		

Conclusions

- Tivozanib and bevacizumab have comparable PFS and ORR when used in combination with mFOXFOX6 in unselected patients with untreated mCRC
- Patients with low NRP-1 have better PFS than patients with high NRP-1
- Patients with Low NRP-1 had longer PFS if treated with Tivozanib than Bevacizumab in combination with mFOLFOX
- A prospective randomized trial comparing Tivozanib to Bevacizumab in patients with low NRP-1 is warranted