Table S1: Biomarkers of Response Currently Used in Cancer Therapy

Biomarker	Treatment	Cancer type	Comments
Estrogen/progesteron receptor	hormone therapies	breast cancer	biomarker of response
HER2 overexpression/ amplification	trastuzumab, lapatinib	breast cancer	biomarker of response
EGFR mutation	erlotinib	lung cancer	EGFR positivity is not predictive
KRAS mutation	cetuximab	colorectal cancer	biomarker of resistance
MGMT methylation	temozolamide	glioblastoma	biomarker of response

Table S2: Current Biomarker Data for Bevacizumab (Bev) Therapy

Type of cancer	Tx	Study Phase	Study size / Time-points	Biomarker findings	Reference
Met BC	Bev + chemo	II	21 pts Baseline	Expression of CD31 and PDGFRβ in tumor vessels by IHC was significantly associated with response Tumor VEGF showed a trend towards association with response pVEGFR2(Y996), pVEGFR2(Y951), MVD, Ki67, apoptosis, grade, ER, HER-2/neu, and p53 - no association	Yang et al., J Clin Oncol 2008
Met NSCLC	Bev + chemo	II/III	n = 56-166 pre and post (week 7)	Baseline sICAM1 but not sE-sel, VEGF, bFGF - strong independent prognostic factor for OS Trend for a substantial benefit from bevacizumab for patients with a drop in sE-sel levels of <5.35 ng/mL at week 7	Dowlati et al., Clin Cancer Res 2008
Ov Ca	Bev + sorafenib	II	n = 42 pre and post (every 2 cycles)	CA125 not a predictive biomarker for targeted therapy	Azad et al, Cancer 2008
rGBM/AA	Bev + chemo	II	n = 60 Baseline	High tumor VEGF, increased RR but not OS High CA9, poor OS	Sathornsumetee et al, J Clin Oncol 2008
Ov Ca	Bev + metronomic chemo	II	n = 70 Baseline	VEGF, E-selectin, and thrombospondin-1 - not associated with clinical outcome	Garcia et al, J Clin Oncol 2008
rGBM	Bev + chemo	II	n = 21 pre and post (week 1/2, 6)	Both early and later FLT-PET responses were more significant predictors of OS (1 to 2 weeks, P = .006; 6 weeks, P = .002), compared with the MRI responses	Chen et al, J CLin Oncol 2007
Met BC	Bev + chemo	III	n = 363 Baseline	The VEGF-2578 AA genotype was associated with a superior median OS The VEGF-1154 A allele also demonstrated a superior median OS Two additional genotypes, VEGF-634 CC and VEGF-1498 TT, were associated with significantly less grade 3 or 4 hypertension in the combination arm	Schneider et al, J Clin Oncol 2008
Met CRC	Bev + chemo	III	n = 312 Baseline	No statistically significant relationship between VEGF, thrombospondin-2 or microvessel density and the increase in median OS	Jubb et al, J Clinc Oncol 2006
Met CRC	Bev + chemo	III	n = 295 Baseline	No statistically significant relationship between mutations of k-ras, b-raf, or p53 and the increase in median OS	Ince et al, J Natl Cancer Inst 2005
aRC	Bev then Bev + chemoradiation then surgery	I/II	n = 32 pre and post (days 3/12 mono, day 33 combo, day 96 pre-surg)	Increase in VEGF, PlGF, sVEGFR2, decrease in IFP and MVD CEA - no correlation Baseline sVEGFR1, extent of PlGF and VEGF increase and pre-surgery CECs - potential predictive biomarkers of response	Willett et al., JCO 2009

Met, metastatic; BC, breast cancer; RCC, renal cell carcinoma; sICAM1, soluble inter-cellular adhesion molecule 1; bFGF, basic fibroblast growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; ER, estrogen receptor; CRC, colorectal cancer; NSCLC, non-small cell lung carcinoma; rGBM, recurrent glioblastoma; Tx, treatment; Ov Ca, ovarian cancer; AA, anaplastic astrocytoma; PFS, progression-free survival; RR, response rate; OS, overall survival; sEsel, soluble E-selectin; FLT-PET, fluorothymidine positron emission tomography; MVD, microvascular density; IFP, interstitial fluid pressure; CPC, circulating progenitor cell; CECs, circulating endothelial cells; CA9, carbonic anhydrase IX

Table S3: Current Biomarker Data for Sunitinib Therapy

Type of cancer	Tx	Study Phase	Study size / Time-points	Biomarker findings	Reference
RCC	Sunitinib mono		n = 26 pre and post (day 28)	High CD1c/BDCA-1(+) myeloid DC frequencies were predictive for tumor regression and improved PFS	van Cruijsen, Clin Cancer Res 2008
RCC (Bev refractory)	Sunitinib mono	II	n = 61 pre and post (day 28)	At day 28- significant increase in plasma VEGF and PlGF and decrease in sVEGFR3 VEGF and sVEGFR3 returned to near-baseline levels after the 2-week off-treatment period Lower baseline levels of sVEGFR3 and VEGF-C were associated with longer PFS	Rini et al., J Clin Oncol 2008
Met BC	Sunitinib mono	II	n = 64 pre and post (day 28)	Increases in plasma VEGF and decreases in soluble VEGFRs and sol. c-KIT	Burstein et al., J Clin Oncol 2008
RCC	Sunitinib mono	II	n = 63 pre and post (day 28)	At day 28- significant increase in plasma VEGF and PlGF and decrease in sVEGFR2 and sVEGFR3 All these markers returned to near-baseline levels after the 2-week off-treatment period	De Primo et al., J Trans Med 2007
GIST	Sunitinib mono	I/II	n = 73 pre and post (day 14)	VEGF increased and sVEGFR2 decreased at day 14 and plasma drug levels. VEGF and sVEGFR2 rebounded towards baseline off treatment Patients with clinical benefit had significantly greater increases in CECs and smaller decreases in monocytes	Norden-Zfoni et al., Clin Cancer Res 2007
HCC	Sunitinib mono		n = 34 pre and post (days 14, 28, 56, 84 and 112)	SDF1α, VEGF and PlGF increased and sVEGFR2, sVEGFR3 and CPCs decreased ın circulation Patients with clinical benefit had significantly greater decreases in Ktrans, IL-6 and sol. c-KIT at day 14 An increase in AFP, sol. c-KIT, SDF1α, sVEGFR1, CPCs or IL-6 at any time-point - rapid progression and/or death	Zhu et al., J Clin Oncol, in press

Met, metastatic; BC, breast cancer; RCC, renal cell carcinoma; Bev, bevacizumab; HCC hepatocellular carcinoma; GIST, gastrointestinal stromal tumors; PlGF, placental-derived growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; Tx, treatment; DC, dendritic cell; PFS, progression-free survival; RR, response rate; OS, overall survival; AFP, alphafetoprotein; CPC, circulating progenitor cell; CECs, circulating endothelial cells; SDF1α, stromal-derived growth factor 1 alpha

Table S4: Current Biomarker Data for Sorafenib Therapy

Type of cancer	Tx	Study Phase	Study size / Time-points	Biomarker findings	Reference
Met RCC	Sorafenib mono (200 or 400 mg) vs placebo	II	44 pts, pre and post (28 d)	High baseline Ktrans - better PFS Ktrans change at 4 weeks not predictive of PFS	Hahn et al., J Clin Oncol 2008
Met PC	Sorafenib mono	II	n = 22 pre and post (after every cycle)	PSA- not a good predictor of response	Dahut et al., Clin Cancer Res 2008
Met RCC	Sorafenib + IFNα	II	n = 80 Baseline	Higher VEGF and PDGF - longer PFS	Tannir et al, ASCO 2008
HCC	Sorafenib mono	II	n = 33 Baseline	pERK correlated significantly with TTP	Abou-Alfa et al, J Clin Oncol 2006

Met, metastatic; PC, prostate cancer; RCC, renal cell carcinoma; Bev, bevacizumab; HCC hepatocellular carcinoma; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; Tx, treatment; PSA, prostate-specific antigen; PFS, progression-free survival; TTP, time-to-progression

Table S5: Current Biomarker Data for Experimental Antiangiogenic Agents

Type of cancer	Tx	Study Phase	Study size / Time-points	Biomarker findings	Reference
NSCLC	Vandetanib with chemotherapy	II	n = 207 Baseline	Low baseline VEGF - lower risk of PD when treated with vandetanib vs gefitinib Low baseline VEGF - lower risk of PD when treated with vandetanib + docetaxel vs docetaxel	Heymach et al., ASCO 2008
NSCLC	Neoadjuvant pazopanib	I	n = 19 pre and post (pre-surgery)	PlGF, IFN-α2, HGF, SDF1α, CTACK, CXCL-10, CXCL-9, RANTES, IL-12; M-CSF and TRAIL increased and sVEGFR2 decreased Correlation between sVEGFR-2 changes during pazopanib treatment and tumor shrinkage	Nikolinakos et al., ASCO 2008
rGBM	Cediranib	II	n = 31 pre and post (days 1, 2, 9, 28, 56, 84 and 112)	SDF1α, VEGF and PlGF increased and sVEGFR2 and CPCs decreased ın circulation Patients with clinical benefit had significantly greater decreases in Ktrans, collagen IV and CECs at day 2 Progression was associated with an increase in SDF1α and bFGF	Batchelor et al., ASCO 2008
Multiple carcinomas	Axitinib	II	n = 298 pre and post (every week, 2-weeks or 4-weeks)	Patients with dBP of equal to or more than 90 mmHg after axitinib showed significantly longer OS	Rini et al., ASCO 2008

*except for patients with advanced pancreatic cancer, who also received Gemcitabine

Met, metastatic; NSCLC, non-small cell lung carcinoma; rGBM, recurrent glioblastoma; PlGF, placental-derived growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; IFNα2, interferon alpha 2; IL-12, interleukin 12; Tx, treatment; PD, progressive disease; OS, overall survival; CPC, circulating progenitor cell; CECs, circulating endothelial cells; SDF1α, stromal-derived growth factor 1 alpha; dBP, diastolic blood pressure