high plasma VEGFA (pVEGFA) and VEGFR2 (pVEGFR2) levels might predict progression-free survival (PFS) benefit in metastatic breast cancer (mBC) pts treated with bev (Avastin®) [Miles et al. SABCS 2010]. An exploratory, retrospective analysis of the AVITA phase III study in mPC was performed to determine the relationship between baseline levels of different angiogenic markers and clinical outcome.

Methods: In AVITA, 607 pts with mPC were randomized to GE+bev 5 mg/kg/2w or placebo until disease progression (PD). The primary endpoint of overall survival (OS) was not met (HR 0.89, 95% CI 0.76–1.06), but the secondary endpoint of PFS was highly significant (HR 0.74, 95% CI 0.63–0.87). Plasma samples from consenting pts (n = 225) were collected at baseline, at cycle 2 and at time of PD and used for analysis of 4 biomarkers (BMs) using a novel multiplex ELISA assay, including VEGFA and VEGFR2. Ten additional angiogenic markers were analysed using SearchLight®. Median baseline levels of BMs were pre-specified as a cut point to categorize pts as low or high; correlation to PFS and OS was explored using simple/multiple regression approaches and subgroup analyses.

Results: Baseline characteristics of pts with BM samples were balanced between treatment groups, although some small differences in demographics were present in the BM vs the overall population. Furthermore, slightly faster PD and shorter OS were seen in the placebo group of the BM vs the overall population. High baseline levels of pVEGFA correlated with better PFS and OS in bev-treated pts vs those receiving placebo (table). For pVEGFR2 a similar correlation was found for OS only. No correlation was found for any other BM analysed.

	HR for PFS	HR for OS
pVEGFA low vs high (n = 222)	0.77 vs 0.52	1.02 vs 0.56
Interaction p value	$p = 0.06$	$p = 0.03$
pVEGFR2 low vs high (n = 224)	0.76 vs 0.56	1.04 vs 0.60
Interaction p value	$p = 0.47$	$p = 0.06$

Conclusions: In this subset analysis, pVEGFA and pVEGFR2 were identified as promising BM candidates for predicting PFS and OS with bev in pts with mPC. These data confirm the potential predictive value of pVEGFA and pVEGFR2 already observed in mBC. Similar findings for pVEGFA were also seen in advanced gastric cancer [Shah et al. submitted ECCO 2011]. Further evaluation of these BM candidates in bev studies across different cancer types should be considered.

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Evaluation of Plasma VEGFA as a Potential Predictive Pan-tumour Biomarker for Bevacizumab

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Background: Identifying patients (pts) who benefit from anti-angiogenics is an unmet need. The majority of bevacizumab (bev) trials include biomarker (BM) sampling, with a focus on plasma VEGFA (pVEGFA), which has shown prognostic rather than predictive value [Bernaards et al. ASCO 2010]. However, recent findings in breast (BC, AVADO), pancreatic (PC, AVITA) and gastric cancer (GC, AVAGAST), with a novel ELISA-based assay favouring shorter isoforms ($VEGFA_{121}$ and $VEGFA_{110}$), suggested potential predictive value [Miles et al. SABCS 2010; Carmeliet et al.; Shah et al. both submitted ECCO 2011]. We used this novel assay to retest residual baseline samples from trials in mCRC (AVF2107g), NSCLC (AVAiL) and RCC (AVOREN).

Methods: Aliquots from plasma citrate baseline samples were re-analysed from 398 (AVF2107g), 859 (AVAiL) and 404 (AVOREN) pts. Median levels of pVEGFA were pre-specified as a cut point to categorize pts as low or high; correlation to PFS and OS was explored using simple/multiple regression approaches and subgroup analyses.

Results: The prognostic value of pVEGFA was confirmed in all 3 trials; pts in the control group with high pVEGFA levels had shorter OS than pts with low levels. However, potential predictive value for pVEGFA was not seen. Table 1 shows key pVEGFA BM results for newly analysed studies plus data from AVADO, AVITA and AVAGAST.

	HR PFS pVEGFA low vs high *Interaction p-value*	HR OS pVEGFA low vs high *Interaction p-value*
AVADO (15 mg/kg)	0.86 vs 0.49 *0.08*	1.07 vs 1.02 *0.55*
AVADO (7.5 mg/kg)	0.96 vs 0.52 *0.01*	1.34 vs 0.87 *0.044*
AVITA	0.76 vs 0.56 *0.06*	1.02 vs 0.56 *0.03*
AVAGAST	0.89 vs 0.64 *0.06*	1.0 vs 0.73 *0.08*
AVF2107g	0.64 vs 0.52 *0.61*	0.70 vs 0.68 *0.95*
AVOREN	0.49 vs 0.67 *0.42*	0.62 vs 0.86 *0.55*
AVAiL (15 mg/kg)	0.96 vs 0.76 *0.13*	0.97 vs 0.98 *0.67*
AVAiL (7.5 mg/kg)	0.77 vs 0.75 *0.77*	0.92 vs 0.89 *0.99*

Conclusions: Results with the novel assay showed potential predictive value for pVEGFA in BC, PC and GC; high baseline pVEGFA levels correlate with improved PFS and/or OS following bev treatment. However, these findings were not replicated in mCRC, NSCLC and RCC. These differences might have been confounded by variations in sample handling (citrate instead of EDTA and increased number of freeze/thaw cycles). As the novel assay has increased sensitivity for shorter VEGFA isoforms, it could be hypothesised that $VEGFA_{121}$ and/or $VEGFA_{110}$ are driving predictive value and might be diverse in different tumour types. Investigation with regard to this hypothesis is ongoing.

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Evaluation of Anti-angiogenic Treatments With DCE-US in 539 Patients − Results After 2 Years Median Follow-up

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Background: A prospective evaluation of dynamic contrast-enhanced ultrasound (DCE-US) with quantification for the evaluation of antiangiogenic treatments was launched in 2007 in 19 French centers, supported by the French National Cancer Institute. The objectives were the diffusion of the standardized method, a cost evaluation and the identification of perfusion parameters predicting tumour response to different anti-angiogenic treatments.

Materials and Methods: All patients had an examination just before the start of the antiangiogenic treatment (D-1) and at D7, D14, D30, D60 and every two months. Each examination included a bolus injection of sonovue (Bracco®) and registration of 3 minutes of raw linear data with an Aplio (Toshiba). Raw data were analyzed with a mathematical model (patent PCT/IB2006/003742) to evaluate 7 parameters characterizing the tumour perfusion curve. The quantification of DCE-US raw data was done without any knowledge of the clinical data. Response to treatment was evaluated every 2 months with RECIST criteria. Complete or partial responses and stabilization were classified as successes, progressions as treatment failures. Patients were considered not evaluable after treatment stop followed by a progression or increase in drug dose followed by a success. Inclusions were closed in March 2010. In order to have sufficient follow-up data, the statistical analysis was performed more than 12 months after the inclusion of the last analyzed patient.

Results: Since October 2007, 539 patients have been included (mainly with renal cell carcinomas (157) and hepatocellular carcinoma (107)). 2368 DCE-US examinations and 1414 scanographic evaluations have been performed. After a median follow-up of 712 days, we confirm that the variation between day 0 and day 30 is significantly ($P < 0.05$) related to DFS for 5 parameters.

Conclusions: Our results confirm the validity of this tool for monitoring antiangiogenic treatments. Decision rules will be proposed to optimize treatment according to the risk of relapse.