

What helps the Clinician in Deciding on Antiangiogenesis Treatment - VEGF/VEGFR?

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Need For Biological Markers

- To develop agents in trials
- To predict which patients may benefit
- To choose most appropriate agents/approaches for particular individual or tumour type
- Approach shown to be beneficial for HER-2 receptor in breast cancer

Problems with Clinical Development of Angiogenesis Inhibitors

- Assessment of optimal biological dose
 - toxicity unlikely until exceed OBD
 - tumour volume reduction unlikely to occur in short term
- Greatest benefit could be on reduction metastasis, slowing tumour growth – difficult to see in Phase I/II.
- Assessment would be greatly enhanced by development surrogate biomarkers of effect

Markers in Targeting Therapy

- Can these be used to predict prognosis?
- Can these predict those most likely to benefit?
 - Reduce potential for toxicity
 - Reduce unnecessary inconvenience
 - Target expensive drugs to those most likely to benefit with improved cost-effectiveness

Potential Surrogate Markers

- Blood: markers of angiogenesis (angiogenic growth factors and markers of activated endothelial cells); pharmacogenetic samples (DNA, RNA and protein levels)
- Tissue: immunohistochemical staining for angiogenesis markers, gene expression and analyses
- Imaging: USS and Gd- MRI scans to evaluate vascular permeability and blood flow

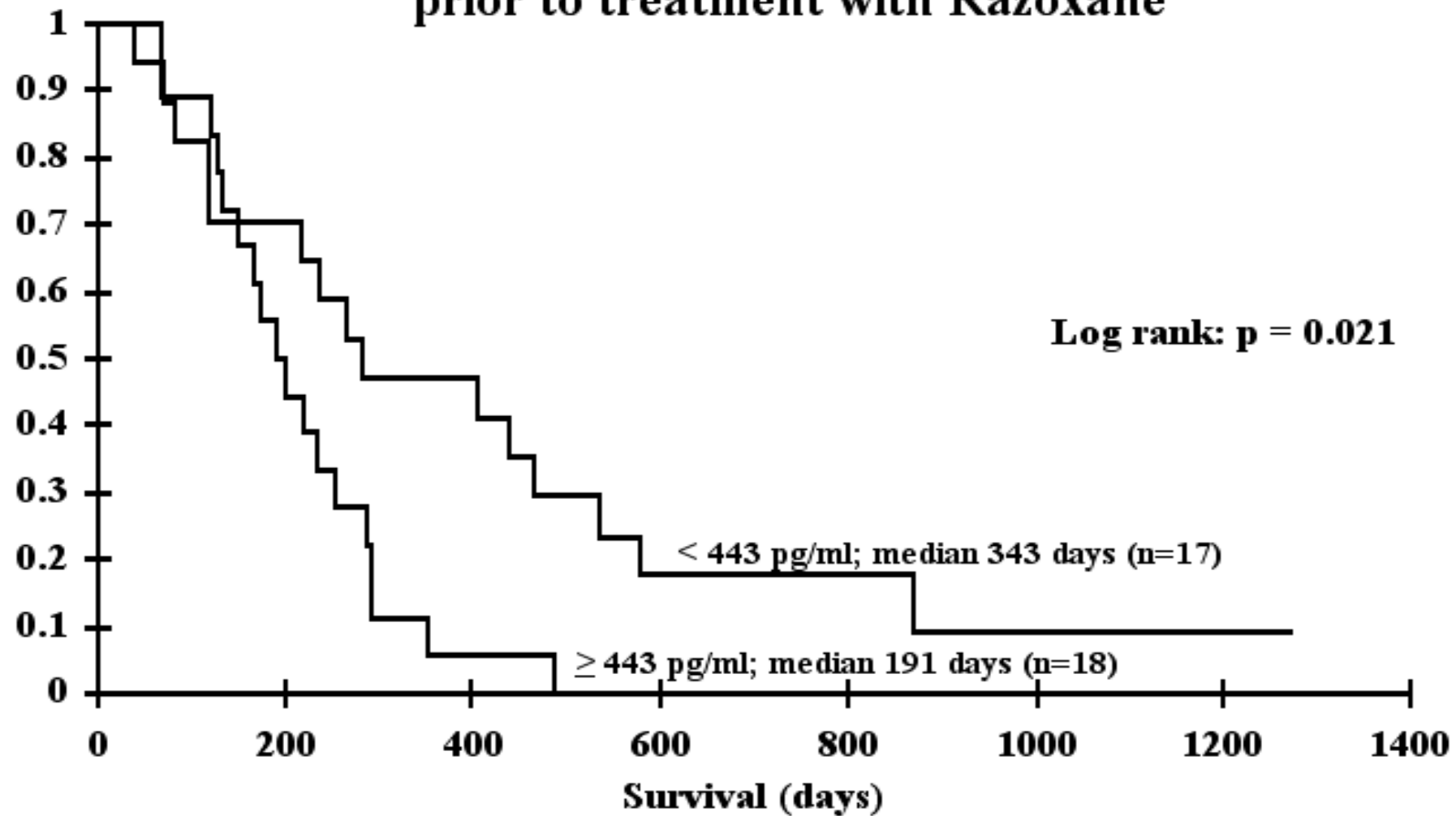
Blood Surrogate Markers

- Markers of angiogenesis (plasma)
 - VEGF
 - bFGF
- Markers of activated endothelial cells (serum)
 - soluble Flt-1 receptors
 - soluble Tie-2 receptors
 - E-selectin

VEGF may be indicator of outcome in CRC

Author	Method	Tissue tested	n	Prognostic value of VEGF level
Amaya et al. 1997	IHC	Tumour	136	Prognostic for overall survival ($p < 0.05$)
Takahashi et al. 1997	IHC	Tumour	27	Prognostic for time to recurrence on UVA ($p < 0.05$). No prognostic value on MVA
Ishigami et al. 1998	NBH	Tumour	60	Prognostic for overall survival ($p < 0.001$)
Maeda et al. 2000	IHC	Tumour	–	Prognostic for recurrence ($p < 0.05$)
Zheng et al. 2003	IHC	Tumour	97	No correlation with prognosis

Survival difference between patients with serum VEGF levels above and below the group median (443 pg/ml) prior to treatment with Razoxane



Predictive Markers

- Highly variable results using many tumour types and markers of angiogenesis
- May reflect different assays and sampling
- May reflect often small sample sizes
- At present no validated measures of factors associated with angiogenesis will confidently predict outcome for any tumour

PTK/ZK: Introduction

- Oral angiogenesis inhibitor
- Inhibits tyrosine kinase activity of the family of VEGF receptors (VEGFR-1, VEGFR-2, VEGFR-3)
 - Less activity against PDGFR- β and c-Kit
- Pharmacokinetic profile compatible with uninterrupted daily dosing
 - Half-life 3 to 6 hours
- Evaluated in 14 phase I/II studies with different cancers and 2 phase III studies in metastatic CRC

PTK787/ZK 222584: Phase I/II Trials

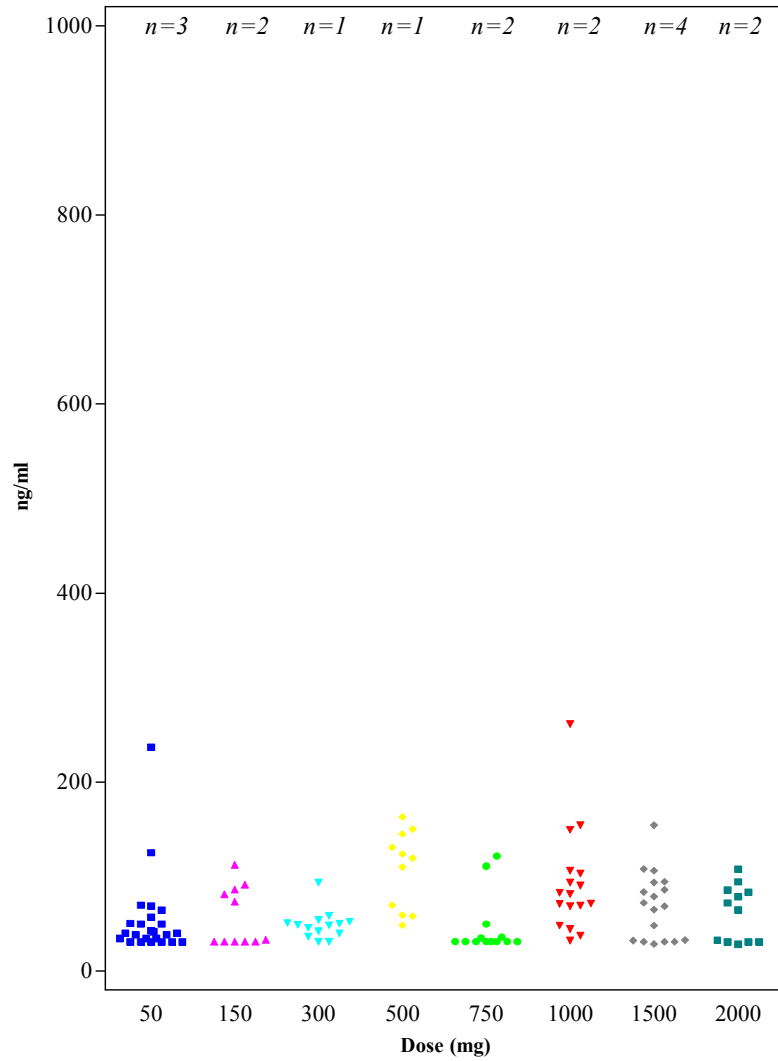
- Studies accompanied by PK/PD
 - Blood markers angiogenesis and activated endothelial cells
- PD included DCE-MRI
 - Provided measure (K_i) of tumour vascular perfusion/permeability
 - K_i correlated with PK and likelihood of reduction in tumour volume
 - Contributed to dose chosen for phase II

Plasma Markers

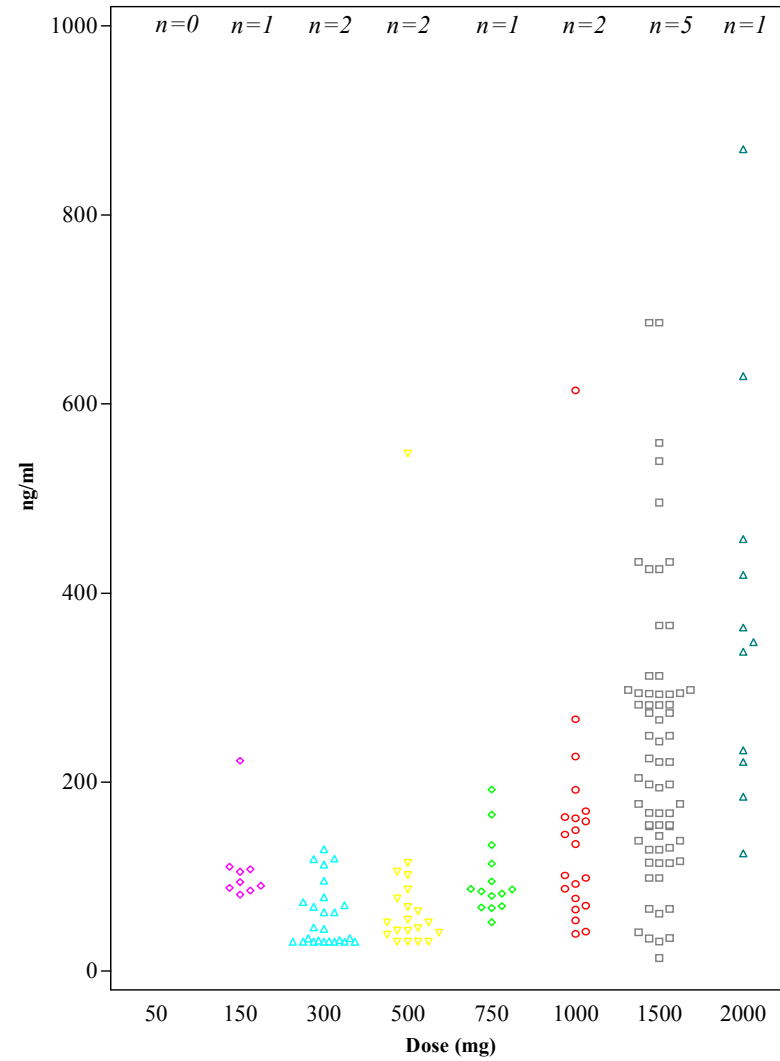
- Early rise in 1st 28 days of VEGF-A associated with significantly greater chance response or SD
- Subsequent fall in VEGF in responders
- May indicate feedback to initial hypoxia and subsequent reduced expression as volume falls
- bFGF, sTIE-2, E-SEL not significantly changed

VEGF-plasma-levels

VEGF - Non Responders



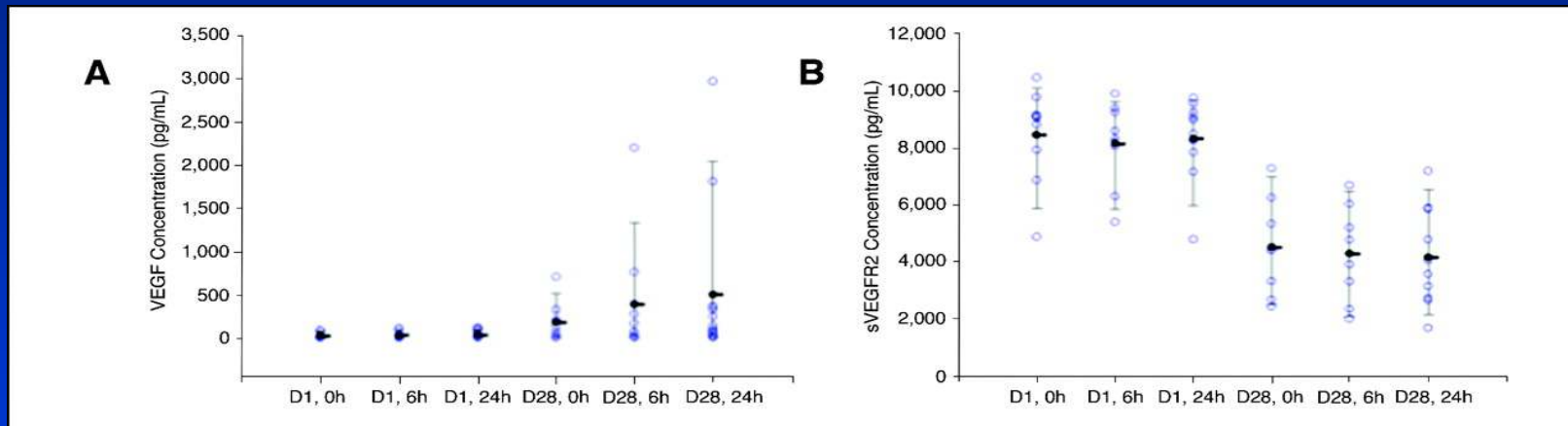
VEGF - Responders



Phase I SU11248 (Sunitinib)

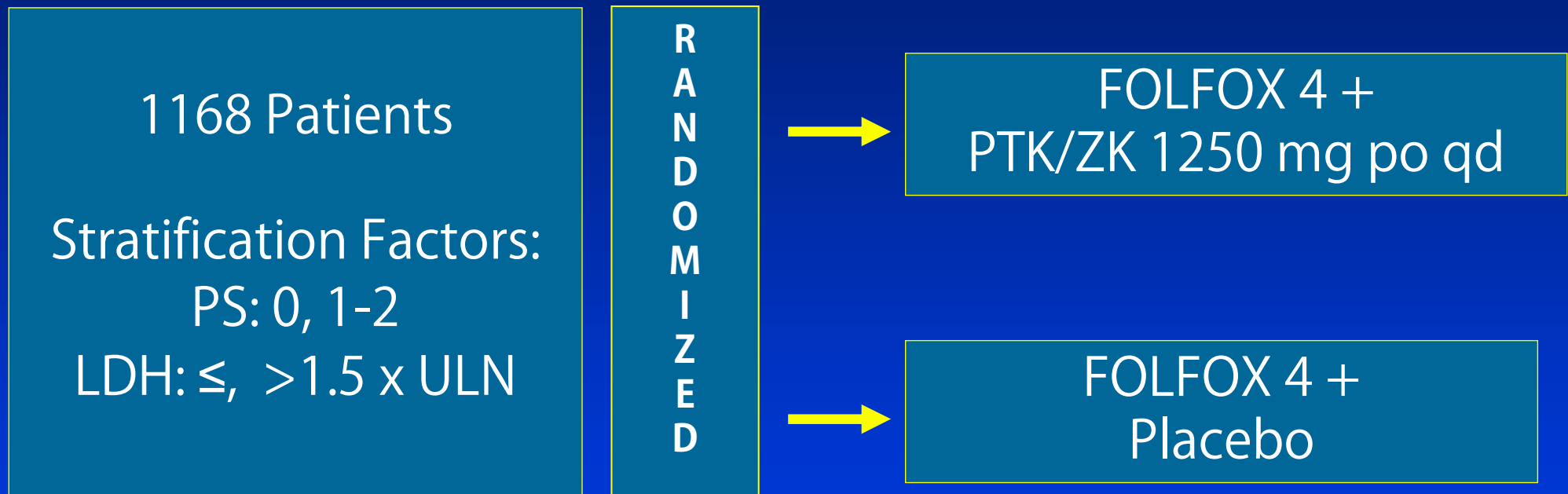
- VEGF-A levels rose during therapy
- VEGF-R2 fell during therapy
- No clear relationship between magnitudes of change and outcomes

Fig 6. Vascular endothelial growth factor (VEGF) concentrations (A) tend to increase after 28 days of treatment with sunitinib (SU11248), whereas; (B) sVEGFR2 concentrations decrease



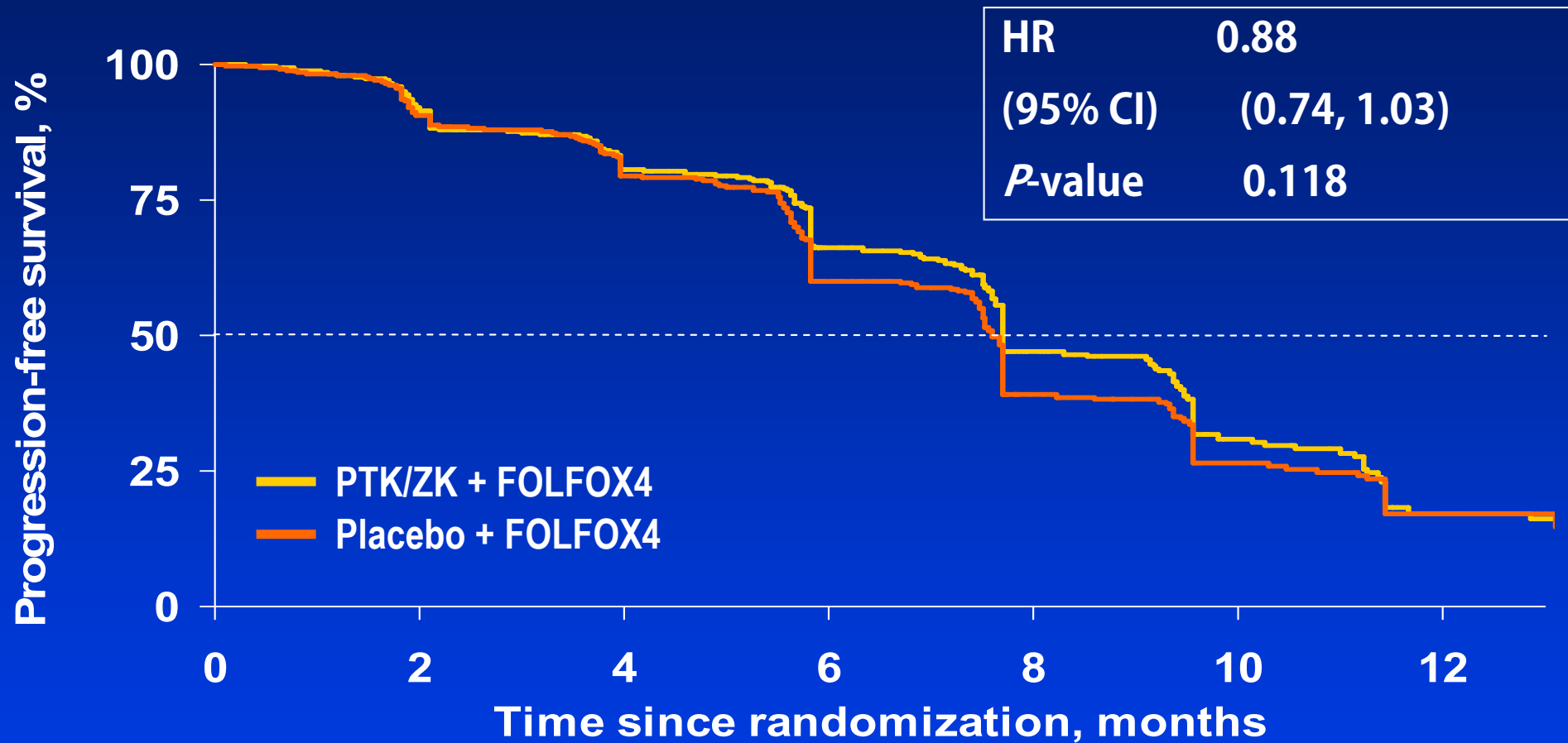
Faivre, S. et al. J Clin Oncol; 24:25-35 2006

CONFIRM-1 Trial Design



Multinational randomized phase III trial in previously untreated mCRC

Progression-Free Survival: Central Assessment (Primary Analysis)*

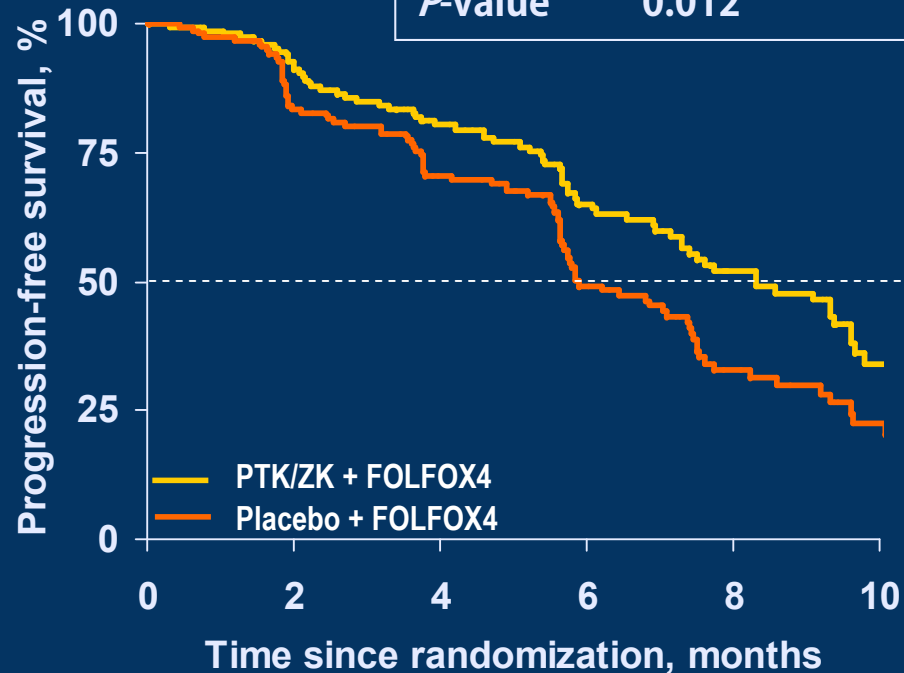


*If assessment is delayed or missed, date of PD is adjusted to previous planned assessment date

Progression-Free Survival: Exploratory Analysis in Patients with High LDH (n=316)

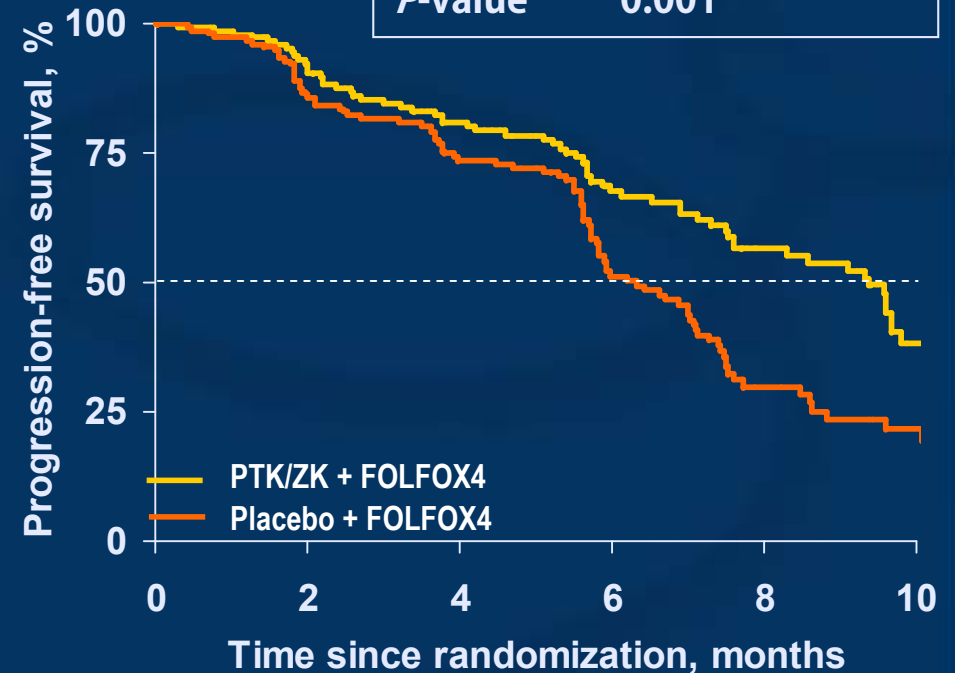
Central Assessment

HR	0.68
(95% CI)	(0.50, 0.92)
<i>P</i> -value	0.012

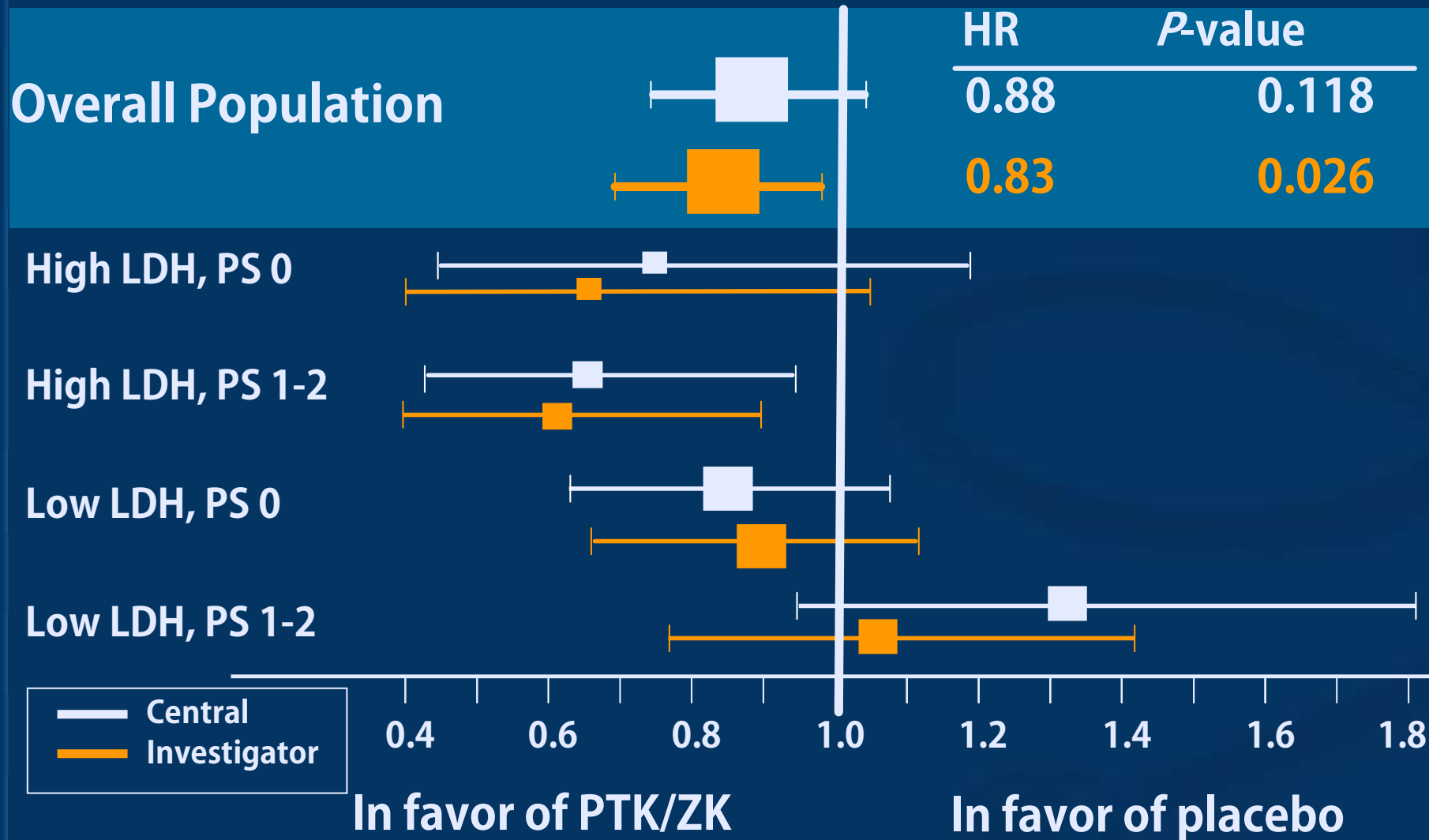


Investigator Assessment

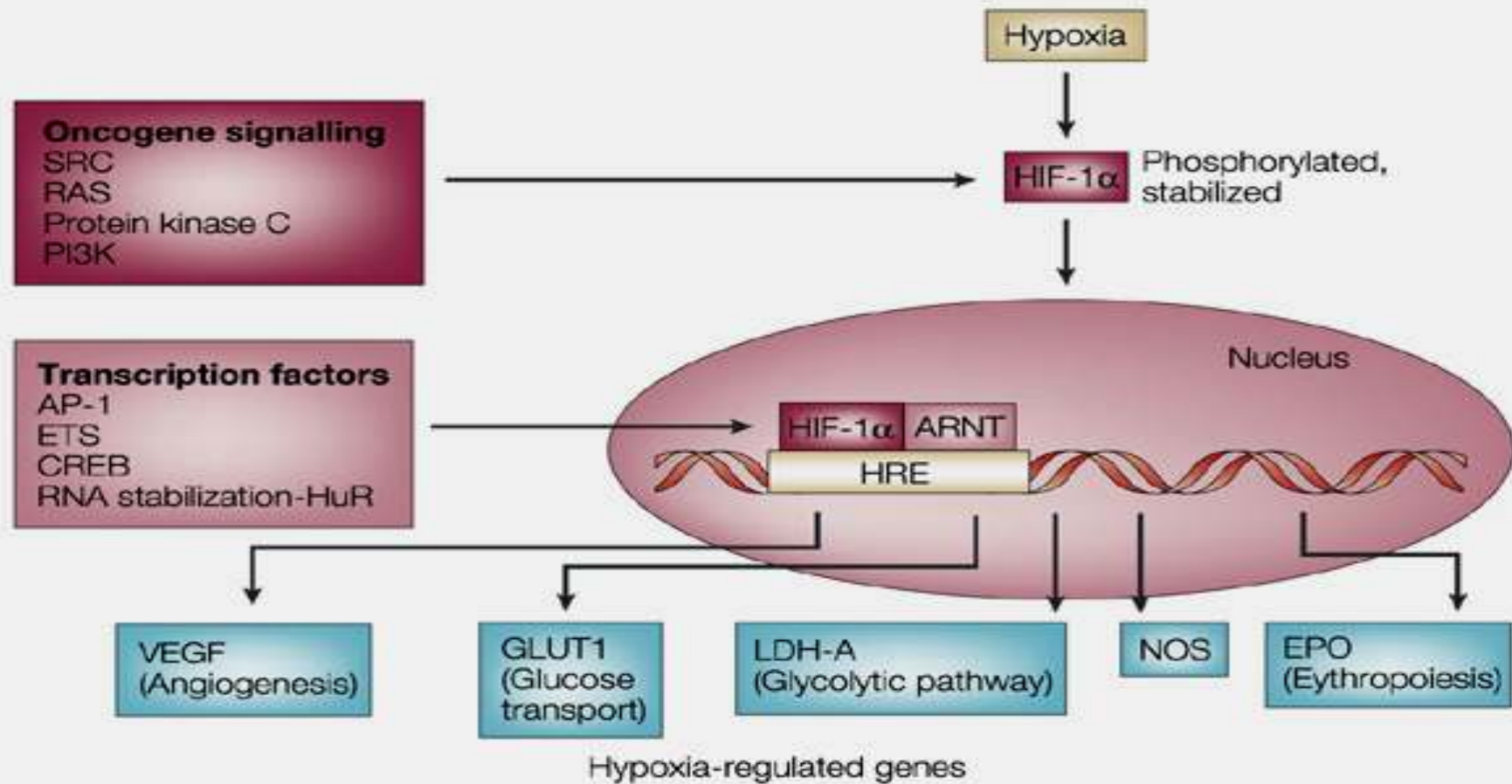
HR	0.60
(95% CI)	(0.44, 0.82)
<i>P</i> -value	0.001



PFS by Pre-Planned Stratum: Hazard Ratio



LDH and Hypoxia



Adrian Harris

LDH: Biologic Implications

Co-regulation of VEGF and LDH via HIF-1 α may provide biologic link for favorable results in high LDH group

Hypothesis:

High serum LDH may predict for both

- poor prognosis and
- optimal benefit from PTK/ZK inhibition of VEGFR

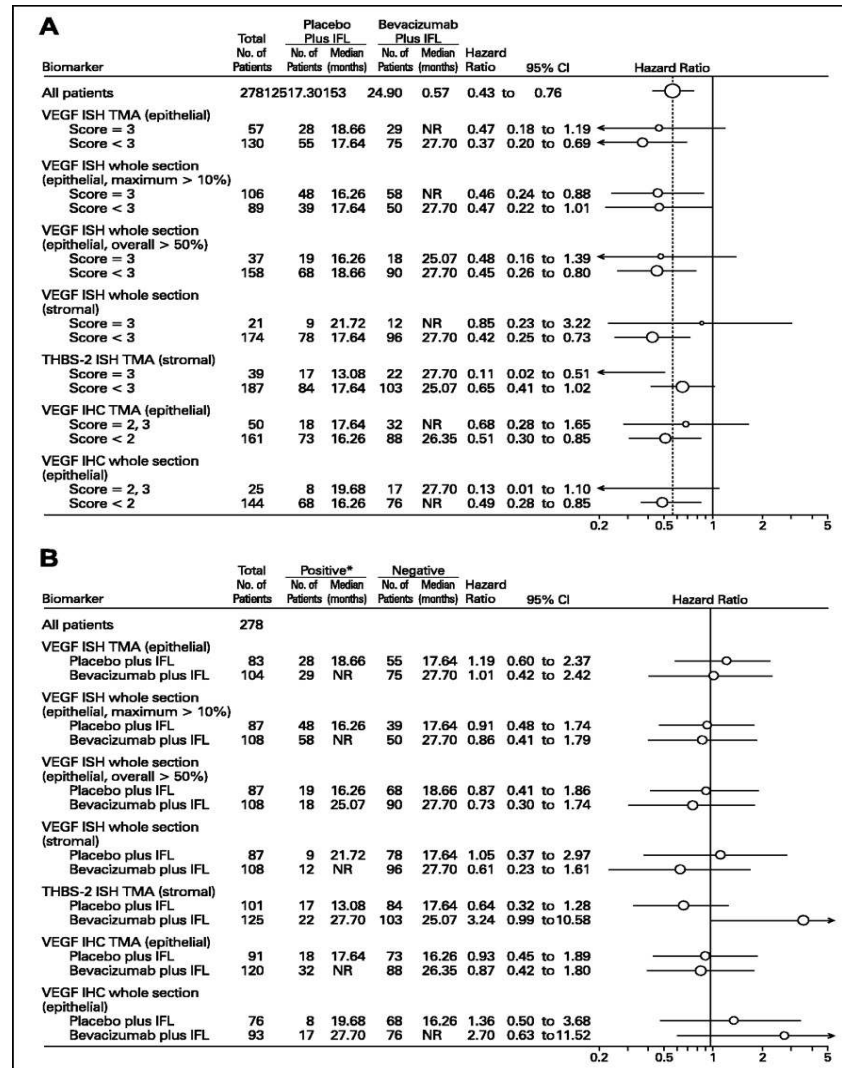
Because:

Patients with high LDH have tumors in which VEGF pathway is most activated

Markers and Outcome in Bevacizumab CRC Trial

- Metastatic CRC 1st line therapy
- IFL +/- bevacizumab
- VEGF, thrombospondin-2, MVD assessed as predictors of benefit from bevacizumab
- 278 patient tumour samples obtained
- No measure significantly predicted outcome or likelihood of response to treatment with bevacizumab

Bubble-grams illustrating predictive (A) and prognostic (B) hazard ratios for risk of death according to (A) biomarker status and (B) treatment subgroup



Summary (1)

- Surrogate markers of effect of angiogenesis on prognosis and response to inhibitors would have clinical relevance and importance
- Although several studies suggest prognosis relates to VEGF, bFGF levels and MVD in many tumours, results conflicting
- Rise in plasma VEGF-A during initial period therapy with receptor TKIs may indicate likelihood of response but requires validation

Summary (2)

- Measures of markers of angiogenesis in tumour specimens does not predict for outcome or response to VEGF antibody bevacizumab in CRC
- Further assays plasma markers in large randomised trials in other tumours may yield prognostic/predictive correlations
- Assays LDH in other studies may yield simple correlative marker of likelihood PFS/survival