

Improving the Quality of Cancer Clinical Trials

Collaboration among Academia,
Pharma, Biotech and Government

Gwen Fyfe, MD

Genentech, Inc.

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Questions for speakers:

- What is the cost benefit of applying expensive technologies versus saving time and improving patient selection with better targeting?
- What are alternative funding approaches?
- What would be the practical results if this approach succeeds?

What is the cost benefit of applying expensive technologies versus saving time and improving patient selection with better targeting?

How much validation and harmonization is required to ensure that expensive technologies will save time and improve patient selection?

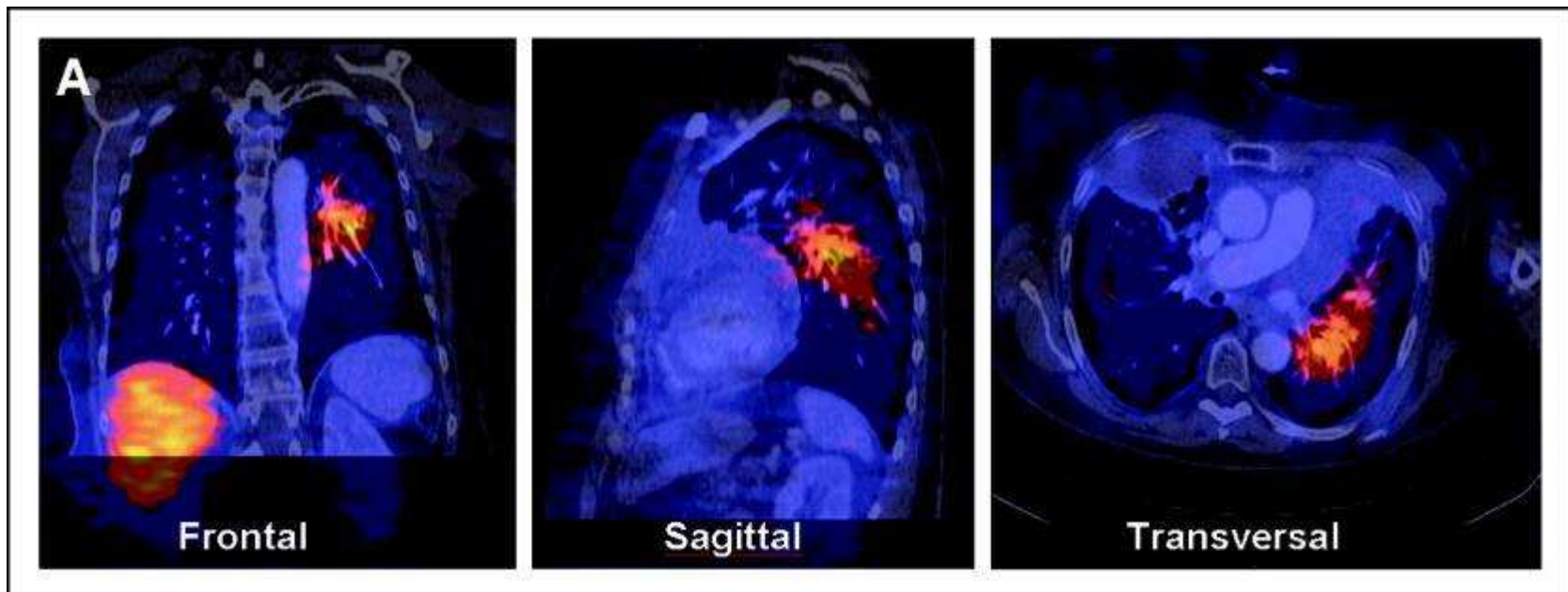
Potential uses of imaging in clinical development of oncology drugs

1. Imaging presence of target on tumor
 - Patient selection
2. Imaging biodistribution of drug
 - How much drug reaches tumor compared to other tissues/organs?
3. Imaging pharmacodynamic changes
 - Imaging biological effect of drug on tumor (or other tissues/organs)
 - Is the drug binding to target?
 - Is the drug inhibiting the target?
 - Is the drug inducing the expected downstream biochemical changes?
4. Imaging surrogate efficacy endpoints
 - Are changes occurring in tumor that are associated with improved outcome (e.g. progression free or overall survival)?

Imaging presence of target on tumor:

^{111}In -labeled trastuzumab and her2+ tumors

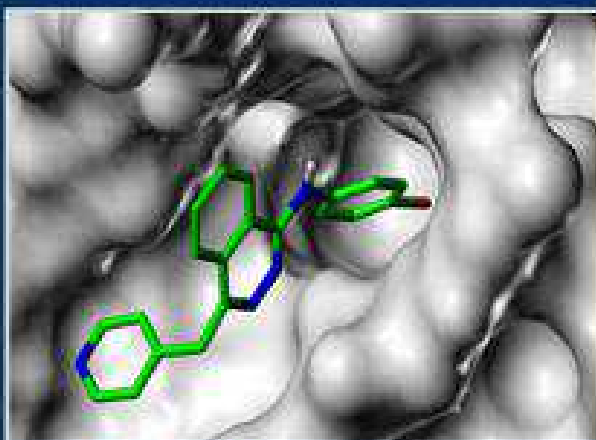
- Single-photon emission computed tomography (SPECT) to image labeled anti-her2 antibody
- Fused CT and ^{111}In -DTPA-trastuzumab SPECT image (96 hours after tracer injection)



Pitfalls

- Interpretation of impact on biomarker
 - Negative predictive value seems likely but positive predictive value low to date
- Surrogate endpoint validation may be disease, pathway and drug specific
- Imaging & diagnostic selection must be validated by accurate prediction of clinical outcome
- What is adequate validation?
 - Validation of technique--reproducibility, site and patient variability, timing of analyses
 - Validation of patient benefit

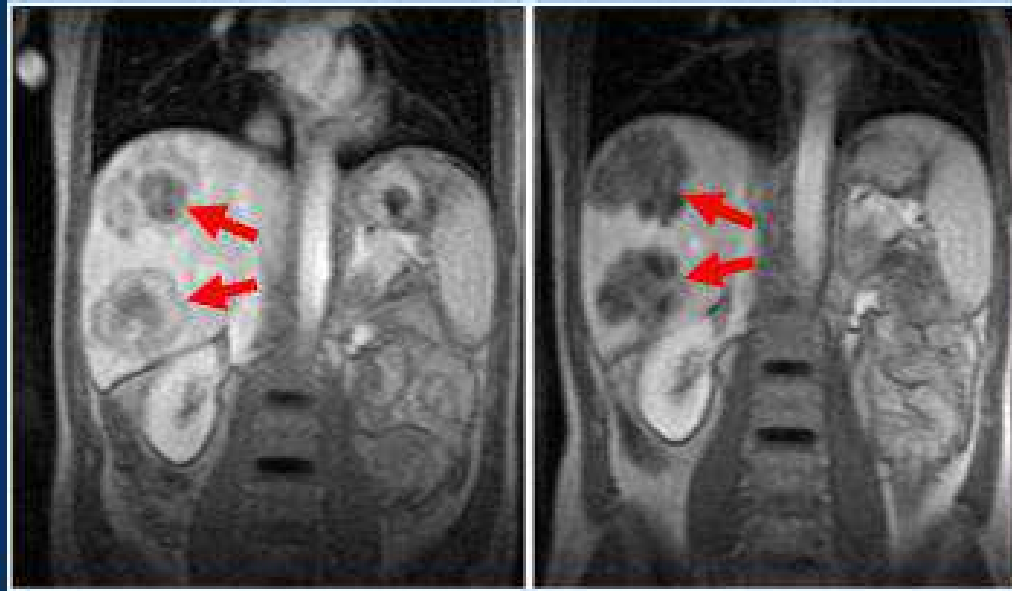
PTK/ZK: An Oral Multi-VEGF Receptor Inhibitor



Fit of PTK/ZK (green)
into the ATP binding site

- Potent inhibitor of all known VEGF receptors
- Also inhibits PDGFR and c-Kit
- Half life of 3 to 6 hours
- Oral once-daily dosing

Proof of Concept in mCRC



Baseline

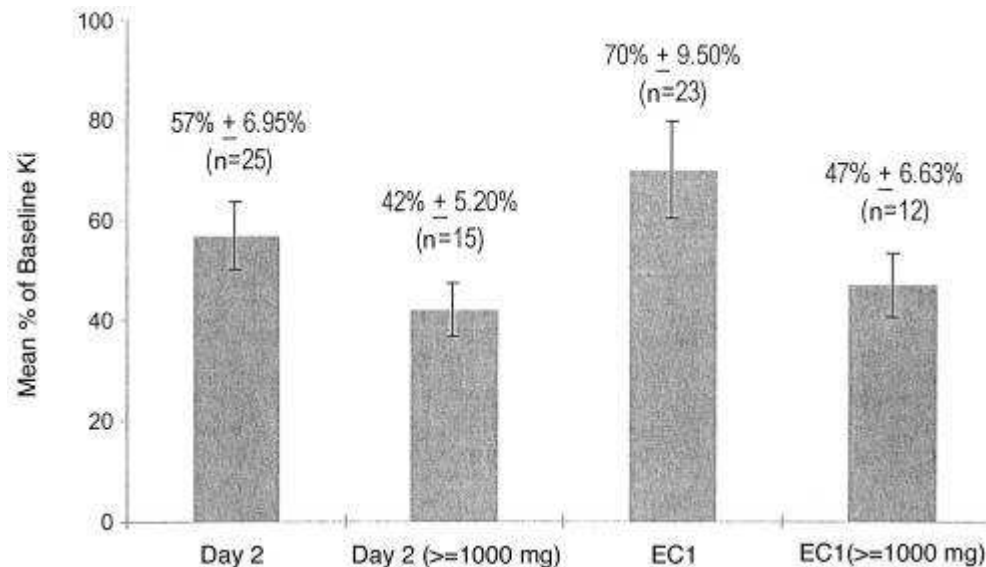
Day 2 PTK/ZK

- Tumor vascularity and permeability decreased rapidly with PTK/ZK and correlated with clinical benefit
- Subsequent PTK/ZK-FOLFOX combination showed promising activity

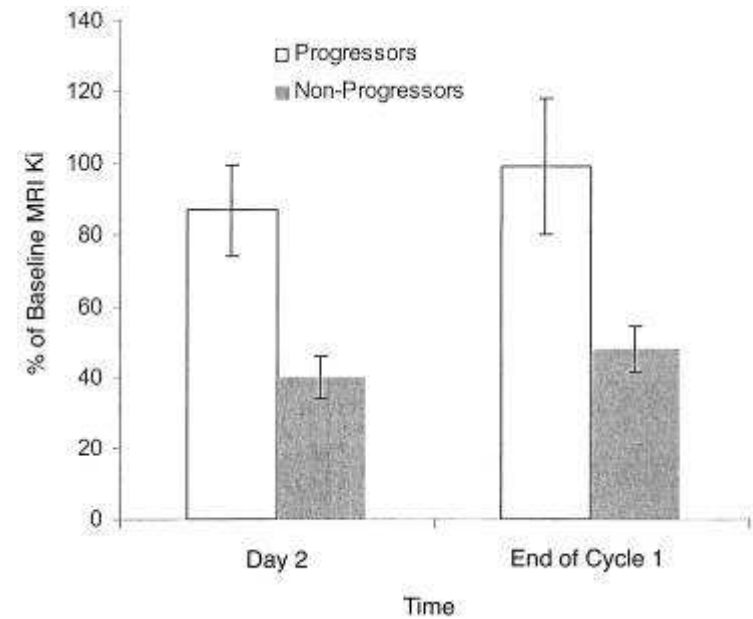
Imaging pharmacodynamic changes: DCE MRI and PTK787

- PTK787 inhibits tumor angiogenesis
 - by inhibiting vascular endothelial growth factor receptor tyrosine kinase
- DCE-MRI: determine bidirectional transfer constant K_i
 - reflects tumor vascularity and permeability

Greater change in K_i at higher doses



Greater change in K_i in non-progressors

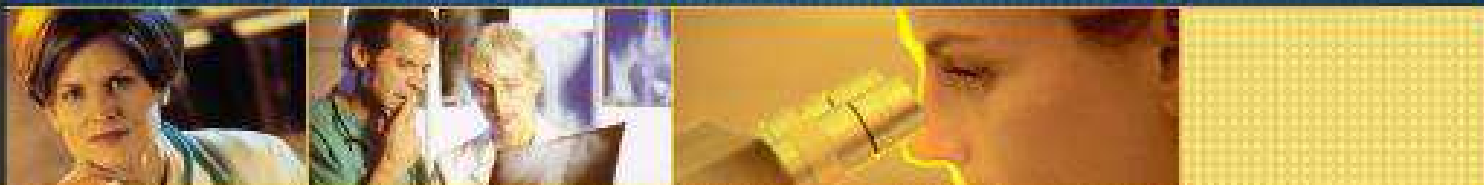


Morgan, B. et al. J Clin Oncol; 21:3955-3964 2003

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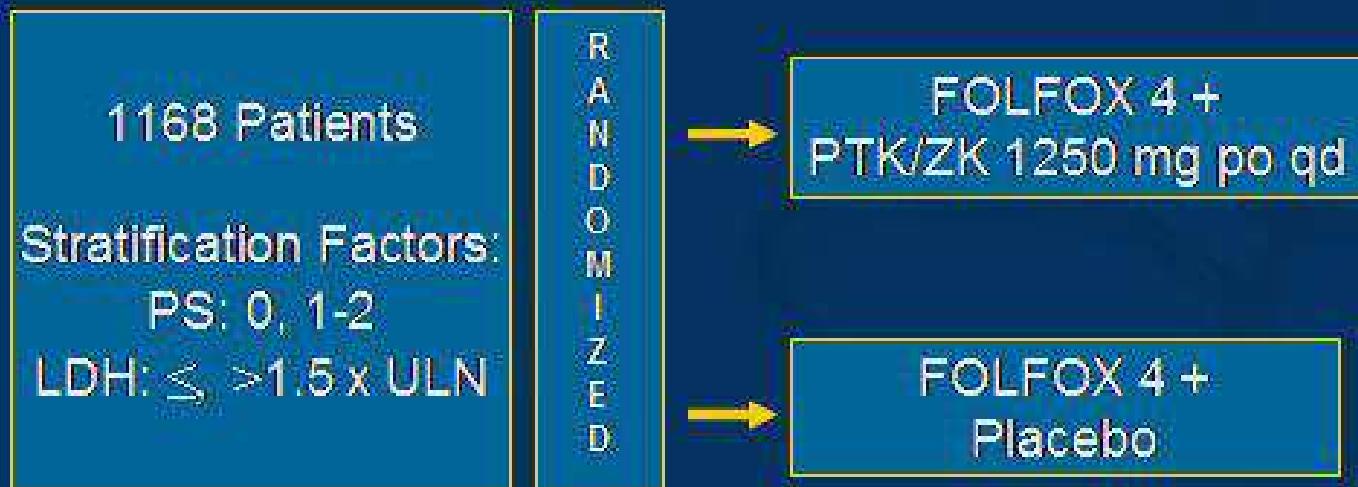
AMERICAN SOCIETY OF CLINICAL ONCOLOGY



**A Randomized, Double-blind, Placebo-controlled
Phase III Study in Patients with Metastatic Colorectal
Cancer Receiving First-line Chemotherapy with
FOLFOX 4 and PTK/ZK or Placebo
(CONFIRM-1)**

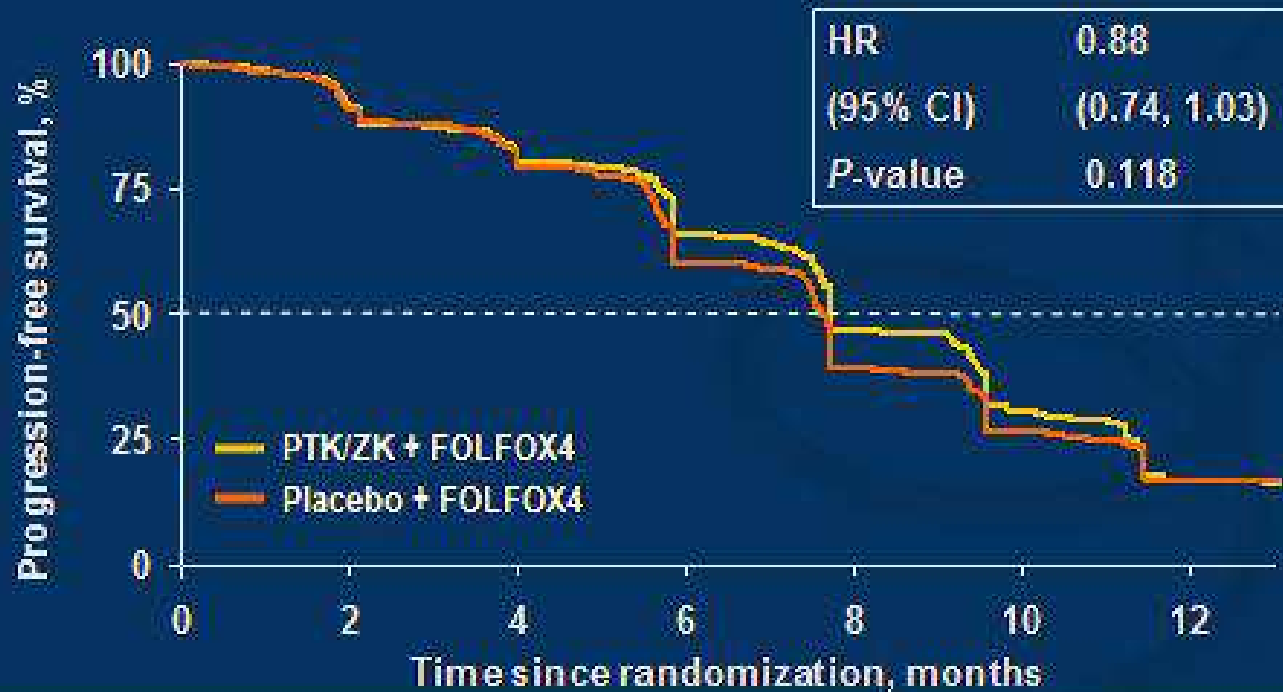
J R Hecht, T Trarbach, E Jaeger, J Hainsworth, R Wolff,
K Lloyd, G Bodoky, M Borner, D Laurent, C Jacques

CONFIRM-1 Trial Design



Multinational randomized phase III trial in previously untreated mCRC

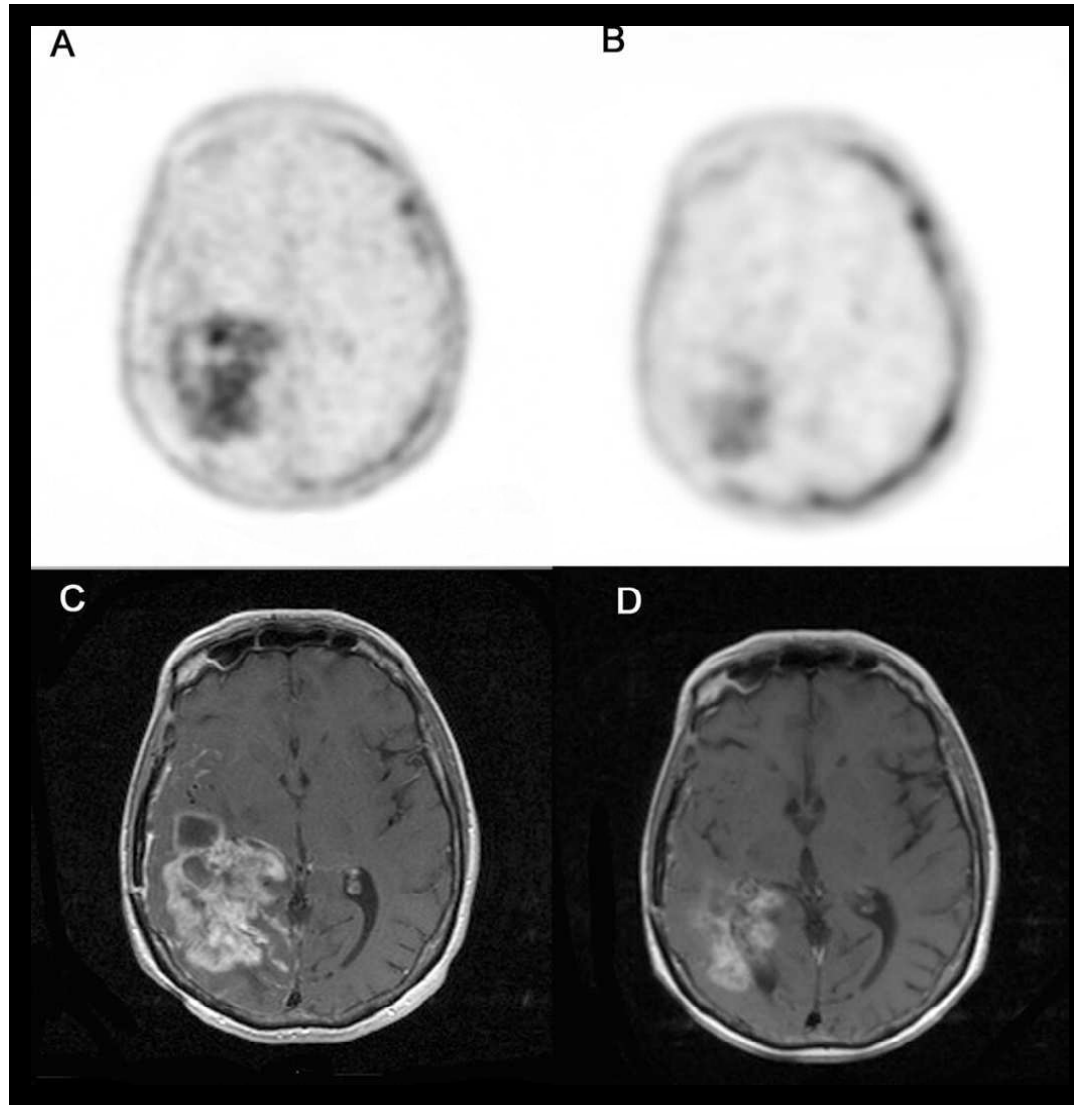
Progression-Free Survival: Central Assessment (Primary Analysis)*



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

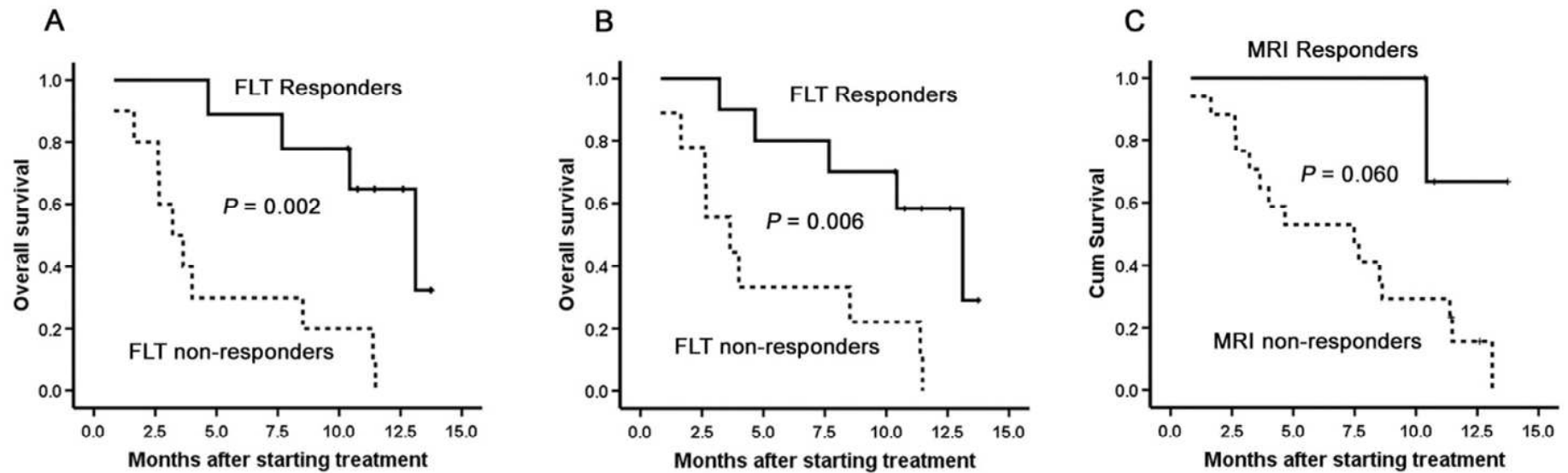
Predicting Treatment Response of Malignant Gliomas
to Bevacizumab and Irinotecan by Imaging
Proliferation with ^{18}F -FLT PET: A Pilot Study

FLT-PET vs MRI in a Responder



Chen et. al. JCO, 2007

Survival by FLT-PET Response



Survival by FLT response at 6 weeks (A), 1-2 weeks (B) or MRI at 6 weeks

CONCLUSION

- FLT-PET as an imaging biomarker appears predictive of overall survival in bevacizumab and irinotecan treatment of recurrent gliomas.
- Whether FLT-PET performed as early as 1-2 week after starting treatment is as predictive as the study at 6 weeks warrants further investigation.

Conclusions (1)

- Expensive techniques save time and improve outcome *only* if carefully validated by clinical outcomes
 - Careful exploratory trials are necessary to assess the best approach to assess impact on biomarkers
 - Validation of imaging techniques within a pathway
 - Even within a pathway agents may differ significantly in their MOA
 - Follow up exploratory trials assessing the relationship of the biomarker effect to clinical outcome will avoid large negative trials
 - Define what clinical endpoints are predictive of benefit....response vs PFS?

Conclusions (2)

- Information sharing across academia, pharma and biotechnology is required to validate surrogates
 - Biomarker Consortium is a start
- Publish both positive and negative results
- Government investment in defining ‘best practices’

*Validated surrogates will significantly decrease
the Phase III failure rate*

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END