

Building the Evidence Base for Value of New Treatments: *Cost Effectiveness Analyses Alongside Cancer Clinical Trials*

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Workshop on the Value in Cancer Care
February 9th, 2009

Values

Providers: Straddling Perspectives

- **Patients and Families**

- Survival
- QOL
- Hope
- Compassion
- Trust
- Recognition of Personhood
- Access
- Communication

- **Payers and Society**

- Survival
- Cost Effectiveness
- Cost Utility
- Innovation
- Efficiency
- Equitability

Oncology Providers:

- Respect
- Professionalism
- Status
- Security

Overview:

- **Cost Effectiveness Analysis in Clinical Trials**
 - **Methods for Conducting CEA Companions to RCTs**
 - **When is CEA Necessary?**
 - **CEA Example: RCT of Laparoscopic Colon Surgery**
 - **Obstacles to Use of CEA in the US**
 - **Predictions about the Future of CEA in US Cancer Research**

Cost-Effectiveness Analyses

- Compares two or more treatments
- Cost Minimization $\text{Cost}_A - \text{Cost}_B$
- Cost Effectiveness: Units are Life Years Gained (LYs)
- Cost Utility: Units are Quality Adjusted LYs (QUALYs)
- Incremental Ratio: ICER

$$\frac{\text{Cost}_A - \text{Cost}_B}{\text{LY}_A - \text{LY}_B}$$

The Cost Effectiveness Plane

	Efficacy is Less	Efficacy is Greater
Cost is Less	?	Dominates Obvious choice
Cost is Greater	Dominated Poor choice	? Typically anticipated Scenario

When Should a CEA Be Performed?

- **Small benefit in large population**
 - Tamoxifen versus anastrozole for breast cancer
- **New treatment strategy is very costly compared to old**
- **High degree of uncertainty about economic impact of treatment**
 - Zoledronic acid versus pamidronate
 - Zoledronic acid: costs twice but shorter infusion, less renal failure
- **Consider for phase III cooperative group trials**
- **Not relevant for early stage studies**

Methods for Conducting CEA Companions to Clinical Trials

- **Prospective Data Collection**
 - Clear specification of both data collection and analysis plan for economic endpoint
 - Clear specification of either data collection or, analytic strategy but not both
- **Retrospective data assembly**
 - From trial sources (eg claims, QOL from participants)
 - From non-trial sources (eg claims from similar patients)
- **“Back of the envelope”**
 - Just the big ticket items
 - Crude estimates that are fast, inexpensive and potentially misleading

Back of the Envelope for Value of Adding Erlotinib to Gemcitabine in Pancreas Cancer:

Miksad JCO 2007

Incremental benefit of adding erlotinib to gemcitabine therapy for pancreas cancer (mean \$ in 2007\$)	
Overall survival	12.8 days
Quality adjusted survival assuming mild symptoms	9.4 days
Quality adjusted survival if severe symptoms	8 days
Lifetime incremental costs per patient:	
Costs of erlotinib	\$10,300
Costs of adverse events	\$780
Costs of extra survival time	\$4100
Total Costs	\$15,200
Costs/L Y	\$410,000/L Y
Costs/QAL Y (mild to severe symptoms)	\$430,000- \$510,000/QAL Y

Challenges in Conducting CEA in US Cancer Clinical Trials

- Economic analysis of the Clinical Outcomes of Surgical Therapy (COST) trial
- Compares laparoscopically-assisted colectomy (LAC) with open colectomy (OC) for colon cancer
- Authors: *J. C. Weeks, H. Nelson, D. K. Romanus, K. H. Long, D. J. Sargent* Presented at ASCO 2008
- Key Methodology Reference:
Integrating Economic Analysis Into Cancer Clinical Trials: the National Cancer Institute-American Society of Clinical Oncology Economics Workbook JNCI Monographs 1998 (24):1-28.

Background of COST CEA Study

- Laparoscopic-assisted colectomy (LAC)
- Potential advantage:
 - Shorter hospital stay
 - Lower costs as a result of shorter hospital stay
 - Smaller scar, greater patient satisfaction
- Potential disadvantage:
 - Higher chance of residual microscopic disease and therefore, cancer recurrence

COST Study Design

- **NCI Sponsored Phase III Cooperative Group Noninferiority RCT**
- **LAC vs open colectomy in resectable colon cancer**
 - **Primary endpoint – time to recurrence**
 - **Secondary endpoints:**
 - **Complications**
 - **Quality of life**
 - **Cost and cost-effectiveness**
 - **Enrollment -- 872 patients from 48 US/Canadian hospitals**

COST Trial results

- **Clinical**

- No difference between arms in rates of recurrence, survival, or complications
- 1 day reduction in median hospital length of stay (LOS) in LAC arm

Nelson et al, NEJM 2004;

Fleishman et al, Annals of Surgery 2007

- **Quality of Life**

- Minimal short-term differences in QOL favoring LAC

Weeks et al, JAMA 2002

Analytic Strategy

- Comprehensive QOL and \$ data collection permitted a complete cost-utility analysis
- *Cost Minimization:* Appropriate given equivalent clinical & QOL outcomes
- *Perspective:* Third party payer
- *Intention to treat:* Patients assigned to LAC but converted to open surgery (21%) were included in the LAC arm
- *Time Horizon:* No difference between arms in late events, examined cost differences thru post-op month 2
- ***Was LAC less expensive?***

Cost Accounting Methods

Collect Resource Utilization, not Costs

Focus on items expected to differ between study arms

- Surgery and anesthesia time
- Inpatient and ICU days
- Use of laparotomy and laparoscopic instruments, cartridges, and reusable and disposable trocars
- Reoperations
- Outpatient visits for surgery-related complications

Convert Resource Utilization to Costs

- Use site-specific data about billing and the ratio of costs to charges
- Both billing and RCCs vary across sites

COST Results:– Resource use

Resource Category	LAC	Open Colectomy	p value
Mean LOS, days	5.5	6.7	<.001
Mean OR time, minutes	166	109	<.001
Cartridges used per pt	3.4	2.5	<.001

No difference in ICU use, reoperations, or readmissions

Results – “Unit costs*”

Resource Category	Academic Center	Community Hospital
Hospital day	1,426	925
Professional component of surgery, LAC	1,676	2,105
Professional component of surgery, open colectomy	1,653	2,065
Technical component of surgery plus fixed OR supplies, LAC	3,454	5,472
Technical component of surgery plus fixed OR supplies, open colectomy	3,204	3,738

Unit Costs Vary Substantially Across Sites

Unit Costs Have Internal Consistency

All costs in 2007 US\$

Results – Cost comparison

	Incremental Cost of LAC (2007 US\$)	
	Unit costs from academic center	Unit costs from community hospital
Hospital days	- 1,665	- 1,083
OR total cost	1,142	3,275
Anesth total cost	89	140
Recovery	10	-16
ICU days	659	333
Reoperation	- 2	- 1
Rehospitalization	- 293	- 189
TOTAL	- 62 [-1,759, 1,608]*	2,454 [1,421, 3,485]*

95% CI calculated using the bootstrap method

Sensitivity analysis

- In the trial, disposable instruments were used in 83% of LAC cases
 - If no disposable instruments had been used, it would have reduced the incremental cost of LAC by \$960
- In the trial, 21% of LAC patients were converted intraoperatively
 - Using unit costs from the community hospital, LAC remained more expensive even if the conversion rate was 0

Lessons Learned from COST Study

- Economically, the choice between LAC and open colectomy consists of a trade-off between higher operative costs and shorter length of stay
- The direction and magnitude of the effect depends on the cost inputs from a given institution
 - LAC is relatively less expensive in institutions with higher “hotel” costs and less costly operative supplies
- If the true opportunity cost of the surgeon’s time is taken into account, LAC is more expensive in most settings
- Innovation and change in cost of OR equipment could easily change the magnitude of this estimate
- Illustrates both feasibility and challenges of conducting CEA alongside trials

How Often Are CEAs Integrated into Cancer Clinical Trials?

- **Most CEAs are conducted and supported by pharma**
 - Variable quality
 - Marketing vs. science
 - Perception of potential for bias
- **Prospective CEAs in NCI Sponsored Studies**
 - Very few
 - No clear funding mechanism
 - Sometimes supported by supplemental funds from pharma sponsors

CEA Companions to Clinical Trials are Challenging

- **CALGB 80303**
 - RCT of gemcitabine plus bevacizumab versus gemcitabine plus placebo
 - Fully embedded economic companion in RCT
 - 2 years to launch
 - Quality of life and cost assessed by interviewing 250/400 trial participants at 4 intervals 8 weeks apart
 - Efficacy endpoint shows no benefit
 - CEA is “dominated” and uninteresting

Economic Companion to 80405 in Metastatic Colorectal Cancer:

- 2002: 3 arm 2000 person RCT of Chemo with either:
 - Cetuximab
 - Bevacizumab
 - Both
- Pharma sponsors provide support to CALGB to fund companion to parent trial
- 2004: Bevacizumab is FDA approved for first line treatment of CRC
- 2005: Study modified to include Bevacizumab in all arms
- 2008: Pharmacogenomics show that only subgroup of patients with wild type kras gene benefit from cetuximab. Study modified to mandate kras testing
- 2009:
 - Data collection is still ongoing
 - No additional funding
 - Complexity is apparent

Insights from Patient Interviews for CEA: CALGB 80405

- Do cancer patients participating in clinical trials worry about the costs of co-pays and paying for their prescription drugs?
- Do they discuss these concerns with their medical oncologists?
- 409 Colorectal Cancer Participants in 80405
- Most interviews in 2006-7
- Interview on Day 1 and again 3 months later
 - What is your level of worry about affordability of your medicines?
 - Have you discussed the affordability of your treatment plan with your medical oncology team?

Clinical Trial Participants' Concerns About Drug Affordability

Degree of Worry About Drug Affordability	N	Discussion with MD About Drug Affordability
Not worried	160 (39%)	YES: 10 NO: 150
A little worried	126 (31%)	YES: 12 NO: 113
Somewhat worried	75 (18%)	YES: 10 NO: 65
Very worried	41 (10%)	YES: 16 NO: 25

Among patients somewhat/very worried about affordability, 77% haven't discussed their concerns with their MD

Many Rejections

- Last 4 RCT Concepts submitted by CALGB to CTEP with fully integrated economic companions have been rejected
- “Not a funding priority”
- “Not clear how this information will be used”
- “If investigators decide to keep the economic component of this trial, no CTEP funding may be used to support these analyses”

Latest Rejection: CALGB Bladder Cancer Study

- **18 weeks of gemcitabine/cisplatin/placebo followed by up to two years of placebo given every 3 weeks**

versus

- **18 weeks of gemcitabine/cisplatin/bevacizumab followed by up to two years of bevacizumab given every 3 weeks**
- **If the intervention arm is superior and leads to decreased PFS, the cost of bladder cancer systemic therapy will increase more than 10-fold.**

Barriers to Integration of CEA into Evaluation of Cancer Treatment

- **Special consents**
 - **Substantial data collection effort is required**
 - **Lack of data systems architecture**
 - **Reluctance of institutions to share cost data**
 - **Investigator suspicion of validity of analyses**
 - **Less developed analytic methods**
 - **Competing priorities**
 - **Sometimes CEA ends up being irrelevant**
 - **Cost drivers can change rapidly**
-
- **Political and regulatory environment**
 - **Cultural preference to avoid “rationing”**

Can Technology Save Us?

- Cultural and professional preference to embrace technology as the strategy to enhance value
- Pharmacogenomics and personalization of cancer treatment
- “The right treatment to the right patient at the right time=high quality care”
- Requires robust evidence base, sophisticated molecular diagnostics, data systems and multidisciplinary providers

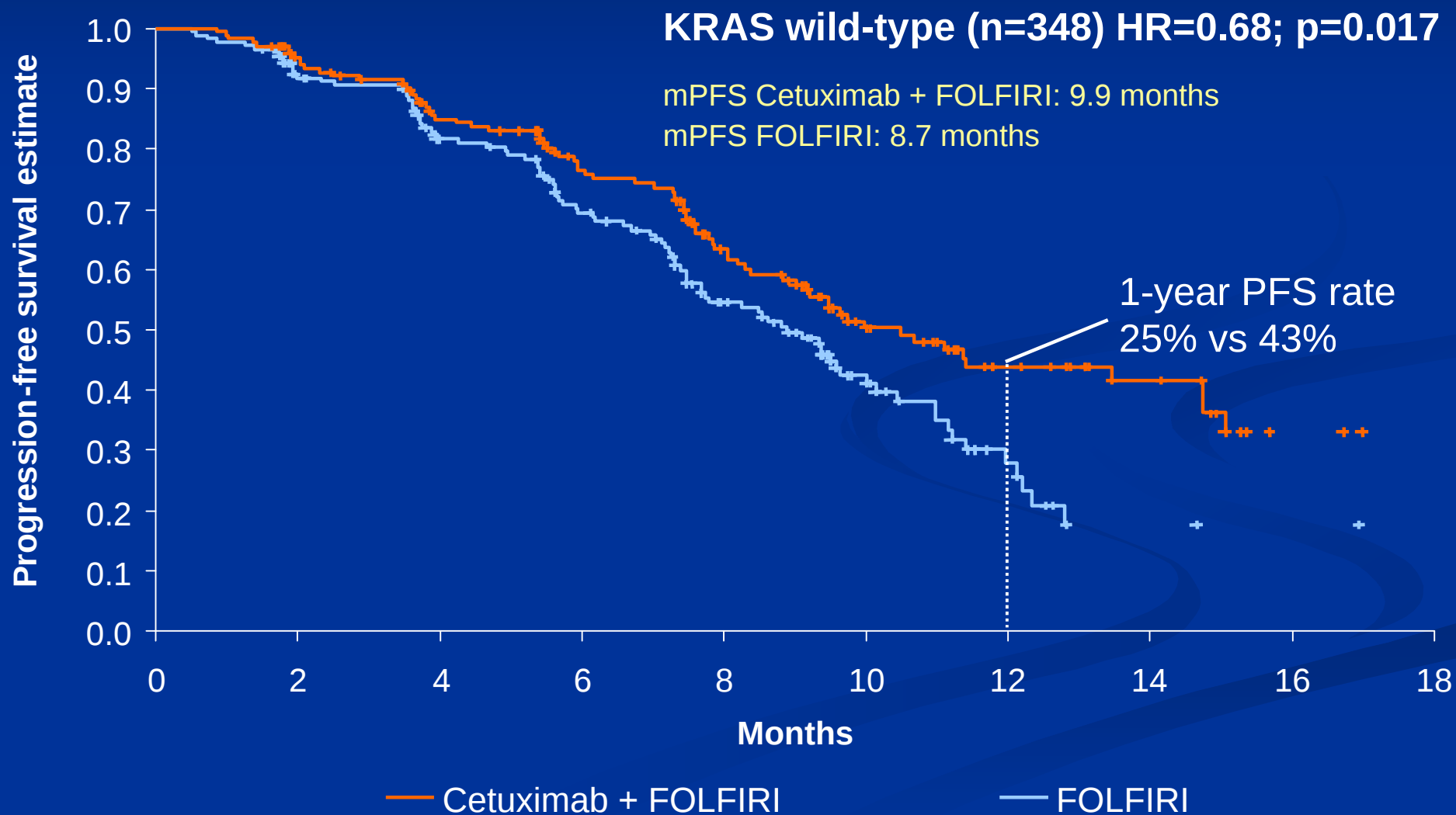
Retrospective Analysis of KRAS status

CRC patients treated on Phase III of FOLFIRI+/-Cetuximab

KRAS population	KRAS wild-type n=348 %	KRAS mutant n=192 %
Age <65	65.8	59.9
Gender, male	57.8	57.8
ECOG PS 0/1	96.6	97.9
Prior adjuvant therapy	21.6	12.5
Involved disease sites ≤ 2	85.3	83.3
Liver-limited disease	19.3	21.9

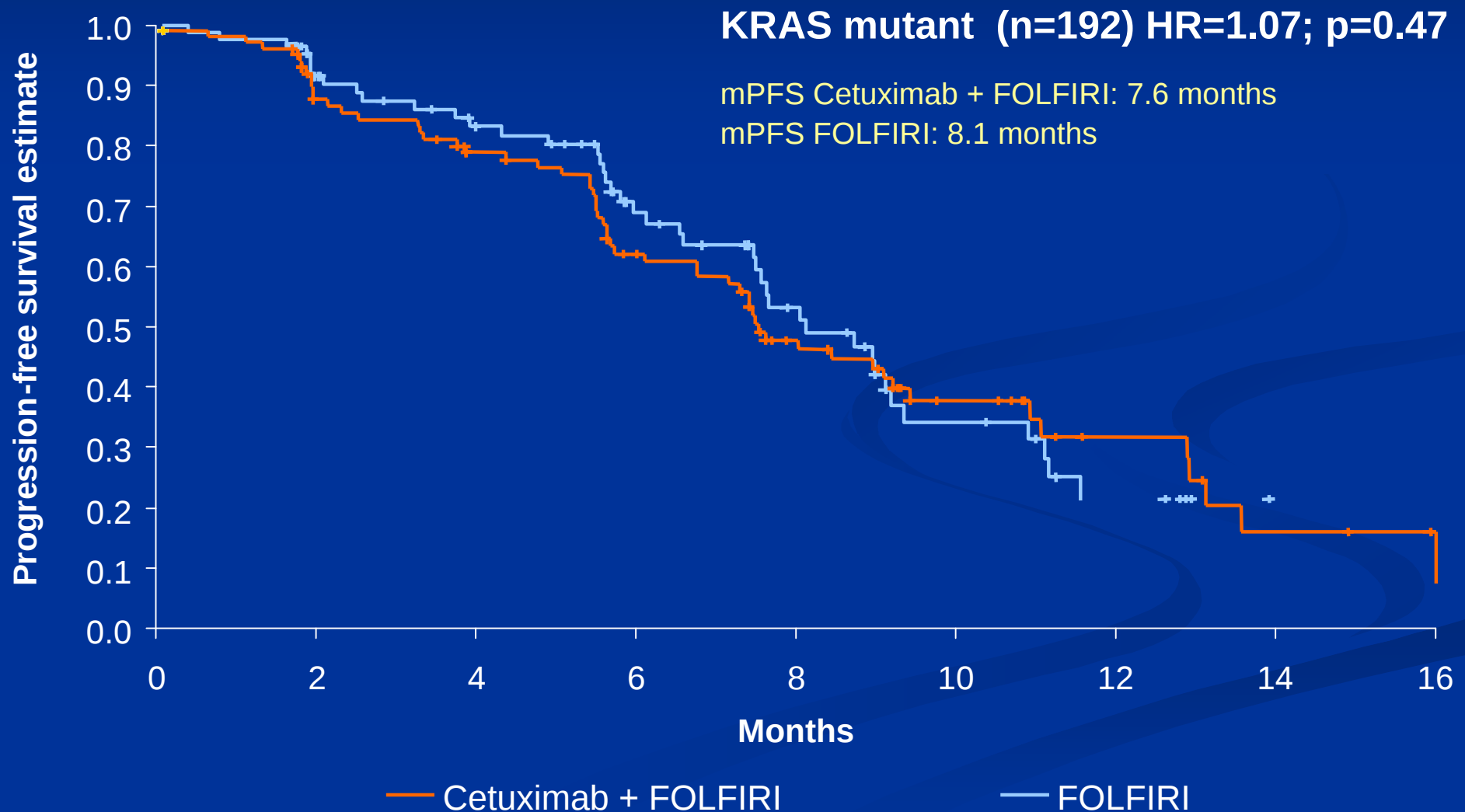
Relating KRAS status to efficacy

Primary endpoint: PFS – KRAS wild-type



Relating KRAS status to efficacy

Primary endpoint: PFS – KRAS mutant

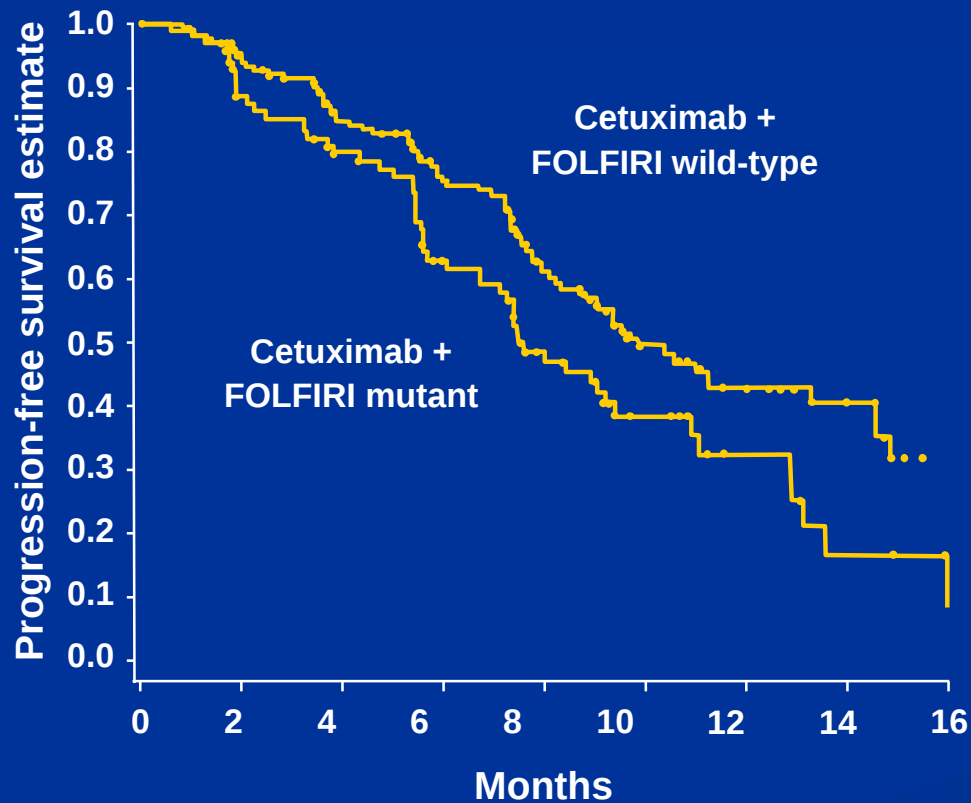


Relating KRAS status to efficacy: PFS

Cetuximab + FOLFIRI HR=0.63; p=0.007

mPFS wild-type (n=172): 9.9 months

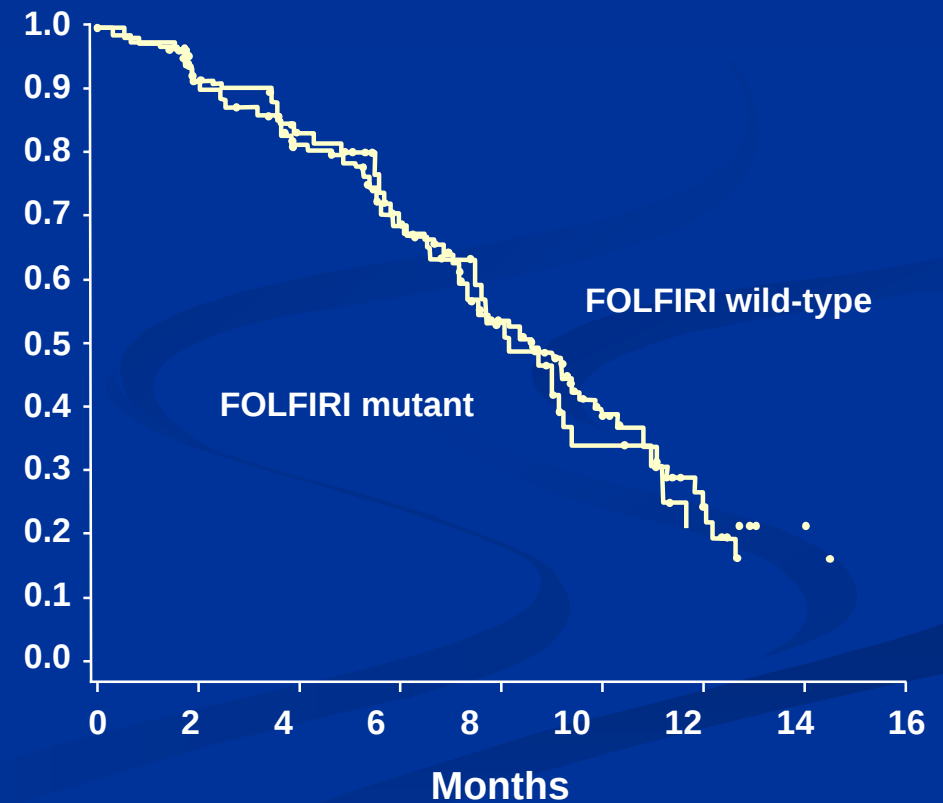
mPFS mutant (n=105): 7.6 months



FOLFIRI HR=0.97; p=0.87

mPFS wild-type (n=176): 8.7 months

mPFS mutant (n=87): 8.1 months



New Challenges:

- **How to tailor treatments to individuals?**
- **Can we withhold treatments that pharmacogenomics tell us wont work?**
 - **Cetuximab for kras mutant colon cancer?**
 - **Herceptin for Her2- breast cancer?**
- **How to build consensus about when to give and when to omit particular treatments?**

Other Strategies to Build the Evidence Base and Increase Value in Oncology

- More information about what works and more guidance based on both evidence and professional consensus:
 - Guidelines
- More information about what we actually do and its consequences
 - Outcomes databases
 - Quality metrics
 - Registries: “coverage with evidence development”
- Limitations on what we are routinely allowed to do
 - Coverage restrictions
 - Compendia
 - Formularies

Personal Viewpoint on Strategies to Enhance Value in Cancer Care

- Only with regulatory reform and changed interpretation of reasonable and necessary will CEA become routine in oncology
- Many strategies to enhance value in cancer care
 - Reform in payment system for new treatment innovations
 - Increase patient engagement through PROs
 - Fundamental reform in system of compensation for cancer providers
- Emphasis on quality, comparative effectiveness, personalization and guidelines is more consistent with our culture

Thank You for your Attention

Reforming Reimbursement for Oncologists

- **Potential Solutions:**
 - Eliminate incentives based on delivery of particular chemotherapy drugs
 - Bundle payment for “episodes of care”
 - Change standards of documentation
 - Incentivize care coordination
 - Incentivize adherence to guidelines
 - Reimburse for information and development of evidence about what works