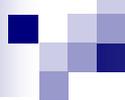


# Regulatory History

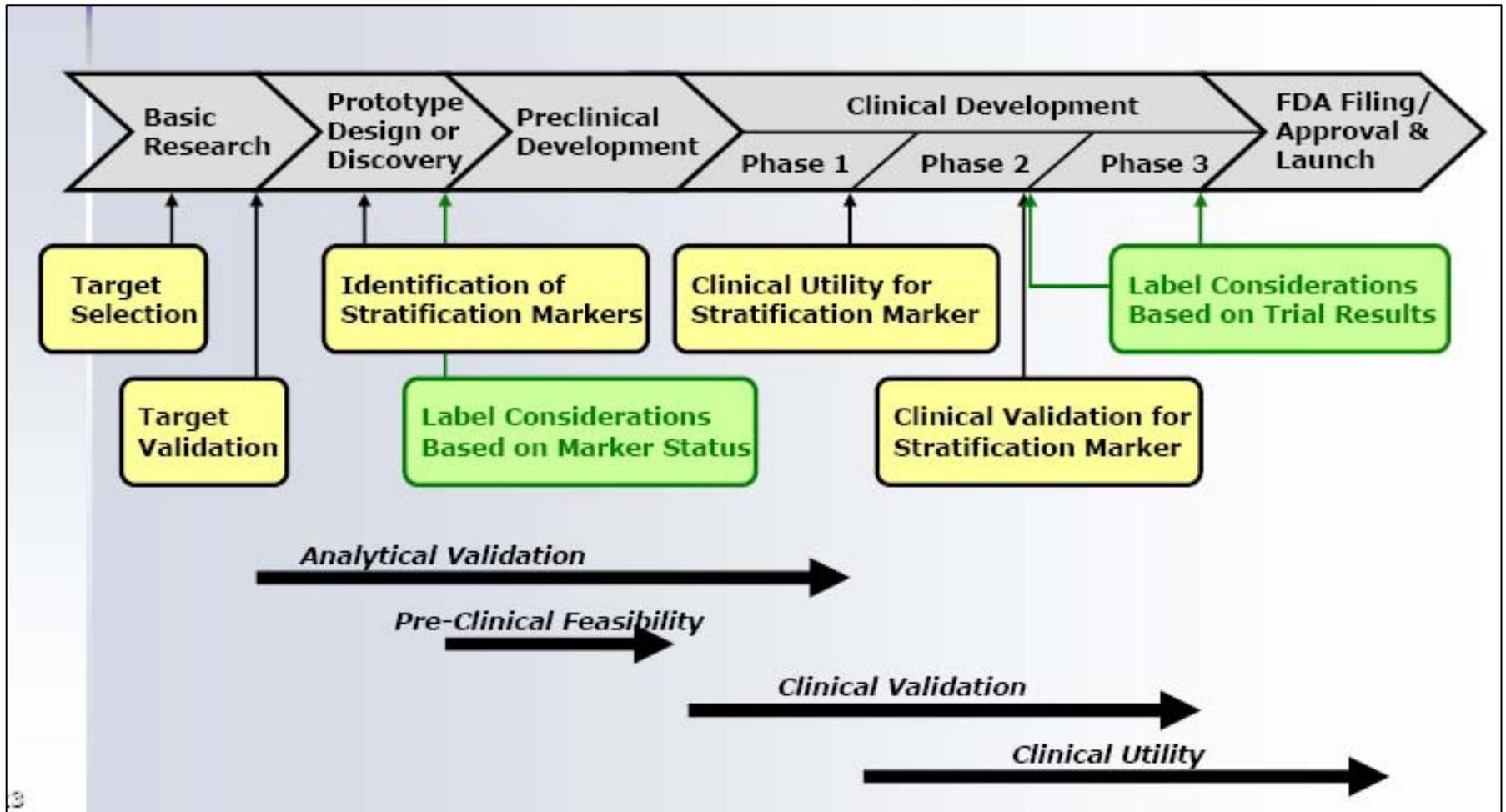
Ruthann Giusti, M.D., Medical Officer  
Div. of Biologic Oncology Products,  
OODP, OND, CDER, FDA

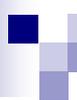


# Genomic Biomarker Directed Therapy

- Limits drug exposure to those who benefit
- Avoid drug use in those who will be harmed
- Optimize drug dosing

# Drug-Test Co-Development





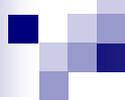
# “Retrospective” Biomarker Assessment

- Incorporate new scientific information
- Not to salvage a “failed” trial

# Anti-EGFR Antibodies

## Approved for Use in Metastatic Colorectal Cancer

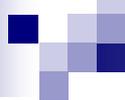
ImClone Systems	Erbitux (cetuximab)
Amgen, Inc.	Vectibix (panitumumab)



# ODAC

## December 16, 2008

FDA seeks guidance regarding how to incorporate new scientific information from a retrospective biomarker analysis without compromising the legal mandate to ensure that marketed drugs show substantial evidence of efficacy and are reasonably safe.



# Retrospective KRAS Analyses

## FDA Advice to the Sponsors:

- Optimal Approach: Conduct an adequate and well-controlled trial, prospectively designed to assess efficacy in subgroups based on KRAS testing by a validated assay.
- Pragmatic Approach: A retrospective analysis could be considered under the following conditions:



# Conditions for Retrospective Biomarker Analysis

1. Adequate, well-conducted, well-controlled trial
2. Large sample size (approximate random allocation of factors not used as stratification variables for randomization, i.e., KRAS status)
3. KRAS genomic status ascertained in a large portion of randomized subjects
4. Assay with acceptable analytical performance
5. Acceptable pre-specified analysis plan

# Cetuximab Randomized Trials

<b>Clinical Trial</b>	<b>Line</b>	<b>Additional Therapy</b>	<b>1° Endpoint</b>	<b>Met 1° Endpoint</b>
<b>CRYSTAL (EMR 62202-013)</b>	1st	FOLFIRI	PFS	YES p-value = 0.048
<b>NCIC-017 (CA225025)</b>	3rd	BSC	OS	YES p-value = 0.005
<b>EPIC (CA225006)</b>	2nd	irinotecan	OS	NO p-value = 0.71
<b>OPUS (EMR 62 202-047)</b>	1st	FOLFOX	RR	NO p-value = 0.06

# Cetuximab Randomized Trials

Clinical Trial	Line	Additional Therapy	Randomized Patients Tested for KRAS			Assay
			n	ITT	% of ITT	
<b>CRYSTAL (EMR 62202-013)</b>	1st	FOLFIRI	540	1198	45	PCR based
<b>NCIC-017 (CA225025)</b>	3rd	BSC	394	572	69	sequencing
<b>EPIC (CA225006)</b>	2nd	irinotecan	300	1298	23	sequencing
<b>OPUS (EMR 62 202-047)</b>	1st	FOLFOX	233	337	69	PCR based

# Panitumumab Randomized Trials

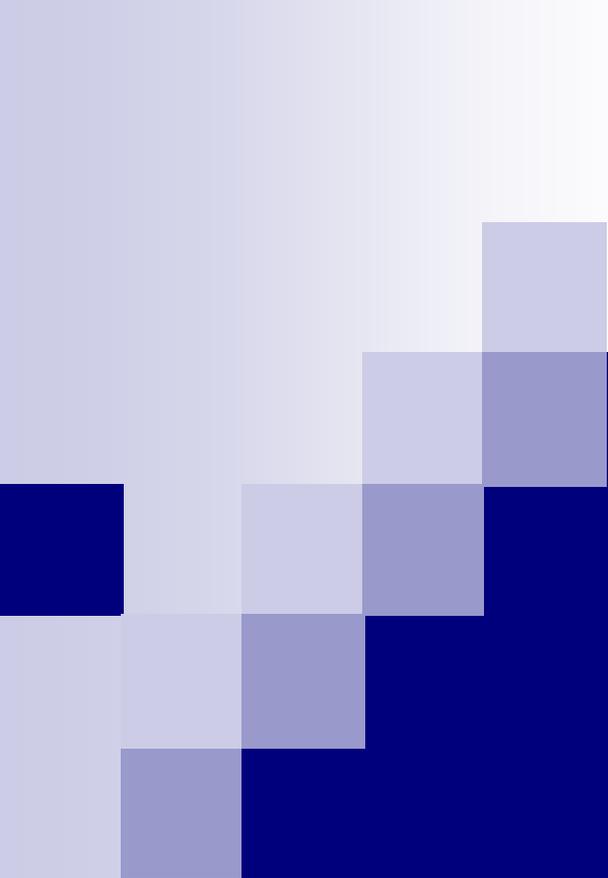
<b>Clinical Trial</b>	<b>Line</b>	<b>Additional Therapy</b>	<b>1° Endpoint</b>	<b>Met 1° Endpoint</b>
<b>20020408</b>	3rd	BSC	PFS	YES p < 0.0001
<b>PACCE (20040249)</b>	1st	chemo/bev	PFS	NO Inferior PFS demonstrated p-value=0.002

# Panitumumab Randomized Trials

Clinical Trial	Line	Additional Therapy	Randomized Patients Tested for KRAS			Assay
			n	ITT	% of ITT	
<b>20020408</b>	3rd	BSC	427	463	92	PCR based
<b>PACCE (20040249)</b>	1st	chemo/bev	863	1053	82	PCR based

# 20020408 Trial: KRAS Status by Treatment Group

<b>Subjects</b>	<b>Panitumumab Plus BSC</b>		<b>BSC Alone</b>		<b>Total</b>	
<b>Randomized</b>	<b>231</b>		<b>232</b>		<b>463</b>	
<b>Included in KRAS analysis</b>	208	90%	219	94%	427	92%
<b>KRAS WT</b>	124	60%	119	54%	243	57%
<b>KRAS Mutated</b>	84	40%	100	46%	184	43%



# Retrospective KRAS Subset Analyses

General Observations

# Retrospective KRAS Subset Analyses

Clinical Trial	Drug	Line	Additional Therapy	1° Endpoint/ Met?		% of ITT KRAS Assayed
<b>CRYSTAL (EMR 62202-013)</b>	Cetux.	1st	FOLFIRI	PFS	YES	45
<b>NCIC-017 (CA225025)</b>	Cetux.	3rd	BSC	OS	YES	69
<b>20020408</b>	Panit.	3rd	BSC	PFS	YES	92
<b>EPIC (CA225006)</b>	Cetux.	2nd	irinotecan	PFS	NO	23
<b>OPUS (EMR 62 202-047)</b>	Cetux.	1st	FOLFOX	RR	NO	69
<b>PACCE (20040249)</b>	Panit.	1st	chemo/bev	PFS	NO	82

# Retrospective KRAS Subset Analyses: 1° Endpoint Time-to-Event

Clinical Trial	Drug	Line	Additional Therapy	KRAS Assayed (%)	1° Endpoint	Hazard Ratio <sup>1</sup> KRAS WT vs. Mutant	
<b>CRYSTAL</b>	Cetux.	1st	FOLFIRI	45	PFS	0.68	1.07
<b>NCIC-017</b>	Cetux	3 <sup>rd</sup>	BSC	69	OS	0.55	0.98
<b>20020408</b>	Panit.	3 <sup>rd</sup>	BSC	92	PFS	0.45	0.99
<b>EPIC</b>	Cetux	2 <sup>nd</sup>	Irinotecan	23	OS	1.29	1.28
<b>PACCE</b>	Panit.	1 <sup>st</sup>	chemo/bev	82	PFS	1.36	1.25

<sup>1</sup>Hazard ratio: Cetuximab vs. no Cetuximab; Panitumumab vs. no Panitumumab

# Retrospective KRAS Subset Analyses: 1<sup>o</sup> Endpoint - Response Rate

Clinical Trial	Line	Additional Therapy	KRAS Assayed (%)	Response Rates (%)			
				WT		Mutated	
				Cetu.	No Cetux	Cetux	No Cetux
<b>OPUS EMR 62 202- 047</b>	1st	FOLFOX	69	61	37	33	49

# Retrospective KRAS Subset Analyses: PFS Endpoint

Clinical Trial	Drug	Line	Additional Therapy	KRAS Assayed (%)	Hazard Ratio <sup>1</sup> KRAS WT vs. Mutant	
<b>CRYSTAL</b>	Cetux.	1st	FOLFIRI	45	0.69	1.07
<b>NCIC-017</b>	Cetux	3 <sup>rd</sup>	BSC	69	0.40	0.99
<b>20020408</b>	Panit.	3 <sup>rd</sup>	BSC	92	0.45	0.99
<b>EPIC</b>	Cetux	2 <sup>nd</sup>	Irinotecan	23	0.77	1.00
<b>OPUS</b>	Cetux.	1 <sup>st</sup>	FOLFOX	69	0.57	1.83
<b>PACCE</b>	Panit.	1 <sup>st</sup>	chemo/bev	82	1.36	1.25

<sup>1</sup>Hazard ratio: Cetuximab vs. no Cetuximab; Panitumumab vs. no Panitumumab

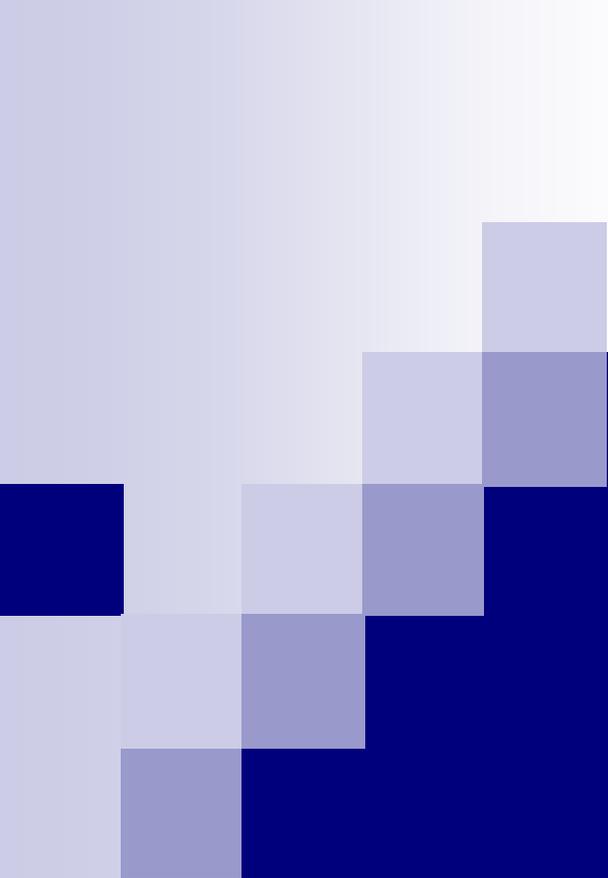
# Retrospective KRAS Subset Analyses: OS Endpoint

Clinical Trial	Drug	Line	Additional Therapy	KRAS Assayed (%)	Hazard Ratio <sup>1</sup> KRAS WT vs. Mutant	
<b>CRYSTAL</b>	Cetux.	1st	FOLFIRI	45	0.84	1.03
<b>NCIC-017</b>	Cetux	3 <sup>rd</sup>	BSC	69	0.55	0.98
<b>20020408</b>	Panit.	3 <sup>rd</sup>	BSC	92	0.99	1.02
<b>EPIC</b>	Cetux	2 <sup>nd</sup>	Irinotecan	23	1.29	1.28
<b>PACCE</b>	Panit.	1 <sup>st</sup>	chemo/bev	82	1.89	1.02

<sup>1</sup>Hazard ratio: Cetuximab vs. no Cetuximab; Panitumumab vs. no Panitumumab

# Ongoing Trials Available for Retrospective KRAS Analysis

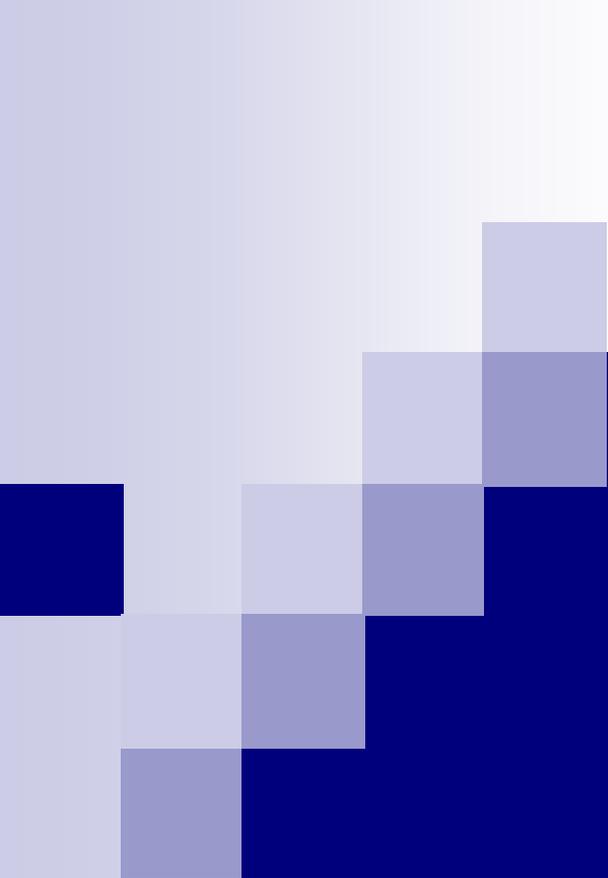
Protocol	Population	Status	Assay
<b>20050203</b>	1 <sup>st</sup> line, mCRC FOLFOX ± panitumumab	Accrual complete (N =1183)	DxS
<b>20050181</b>	2 <sup>nd</sup> line mCRC FOLFIRI ± panitumumab	Accrual complete (N = 1187)	DxS
<b>CALGB 80405</b>	1 <sup>st</sup> line mCRC, 3-arm, 2 x 3, RCT FOLFIRI or FOLFOX with <ul style="list-style-type: none"> <li>•bevacizumab (Arm A)</li> <li>•cetuximab (Arm B)</li> <li>•bevacizumab +cetuximab (Arm C)</li> </ul>	Ongoing > 1400/2289 subjects enrolled	DxS
<b>N0147</b>	2-arm RCT of FOLFOX ± cetuximab for adjuvant treatment of Stage III colon cancer	Ongoing 2344/2650 enrolled; ↑ sample size to 3768	DxS



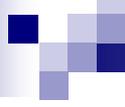
For Further  
Discussion

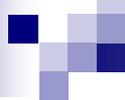
# ODAC December 16, 2008

■ Industry Presentations	ImClone/Amgen
<b>Additional FDA Presentations:</b>	
■ Considerations for optimal drug- device co-development	Robert L. Becker, Jr., MD, PhD Chief Medical Officer, Office of In Vitro Diagnostics, CDRH
■ Considerations for establishing efficacy in support of regulatory marketing and promotional claims	Robert O'Neill, PhD Director, Office of Biostatistics, Office of Translational Science CDER



# Questions for ODAC

- 
- When would it be appropriate to limit use of a drug to a subgroup based on retrospective analysis of one or more studies that were not designed to examine this subgroup?
  - When would a prospective study, designed for the purpose of examining treatment effects on a pre-specified subgroup, be needed to establish treatment effects in this group?

- 
- Discuss the properties of clinical studies, originally designed for non-selected populations, that would make such studies unsuitable for demonstrating efficacy in a biomarker subgroup.
  - When is it acceptable to limit future enrollment to a biomarker selected subset of an actively accruing clinical trial based on external information (e.g., results from another study)? What would be the primary analysis population? Would the answer depend on the proportion of unselected patients, i.e., those enrolled prior to the study modification?

- 
- Please discuss the importance of timing and rigor in determining the analytic performance of the companion diagnostic test.