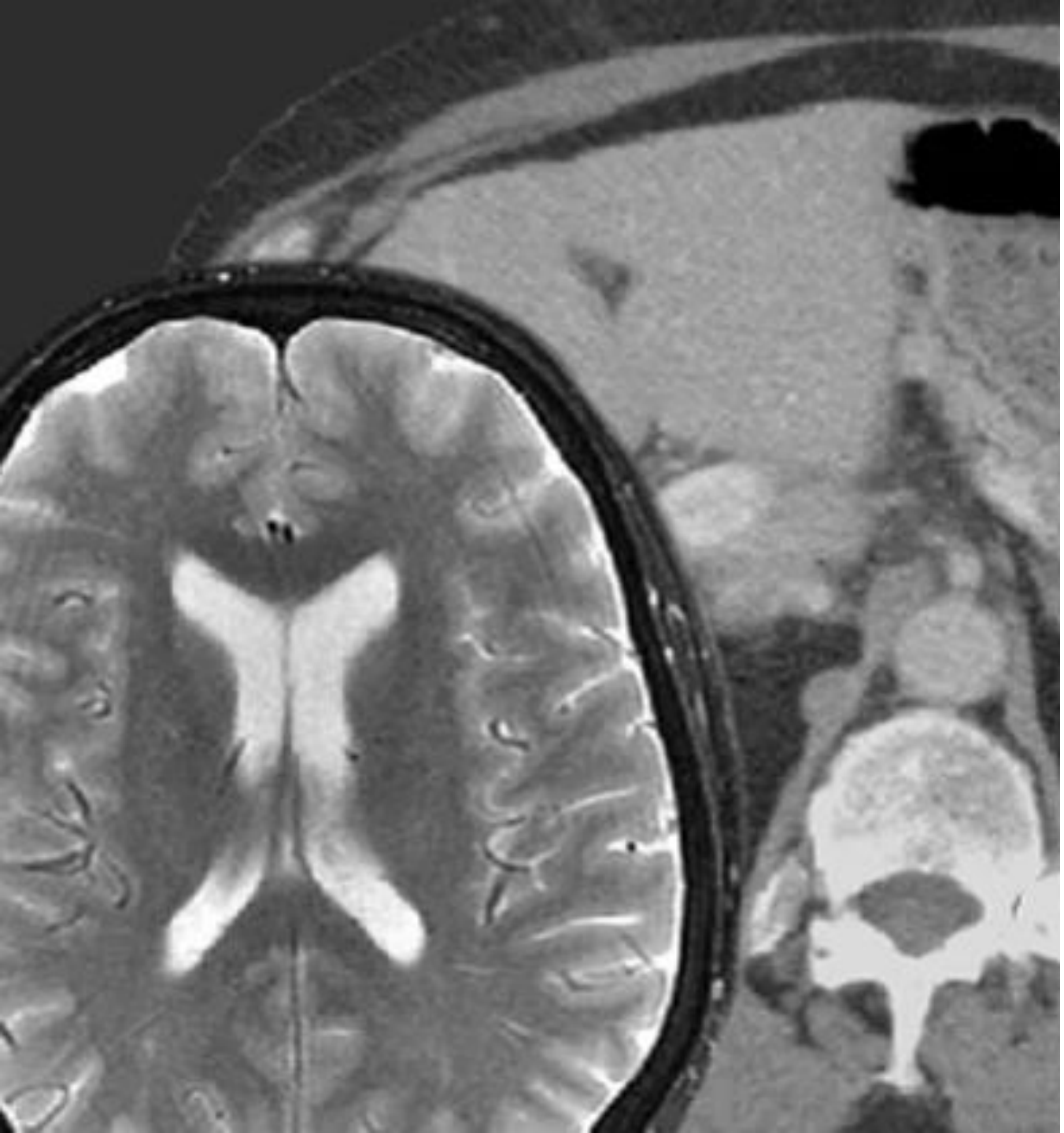

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Codebreak 200 trial - FDA review and ODAC meeting: lessons learned

PINTaD Meeting 26th January 2024

Jayant Narang, MD
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Agenda

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- Code Break 200 ODAC Discussion- Introduction, Background and Key issues
- Lessons Learned - Panel Discussion

The study design, results and analysis slides are borrowed from the ODAC briefing documents and presentations by FDA and Amgen.

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Introduction and background

Annette Schmid, PhD
Sr Director Global Science Policy
Takeda Pharmaceutical Company Limited

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U.S. FOOD & DRUG ADMINISTRATION

Sotorasib for KRAS G12C Mutated Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer

Oncologic Drugs Advisory Committee Meeting
October 5, 2023

Harpreet Singh, MD
Director
Division of Oncology II

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Study background, Issues raised by FDA: Investigator Bias, COP procedure, Global BICR re-read

Jayant Narang, MD.
Senior Medical Director, Clinical Oncology Imaging Lead
Takeda Pharmaceutical Company Limited

CodeBreaK 200: Open-label Trial Design

ACCELERATED APPROVAL

CodeBreaK 100
PHASE 2

Global,
single-arm trial
in patients with *KRAS p.G12C*-mutated
locally advanced or metastatic NSCLC
who have received
at least 1 prior systemic therapy

Sotorasib
N=126

Key Eligibility Criteria
- KRAS G12C mutation
- Advanced / metastatic NSCLC
- ≥1 prior therapy (including chemo and IO)

Stratification Factors
- No. of prior lines of therapy
- Race (Asian vs non-Asian)
- History of CNS involvement

R
1:1

Sotorasib 960 mg daily
N=171

Docetaxel 75 mg/m^2 Q3W
N=174

Crossover*

Sotorasib
960 mg daily

Primary endpoint: PFS per BICR
Secondary endpoints: OS, ORR, DOR

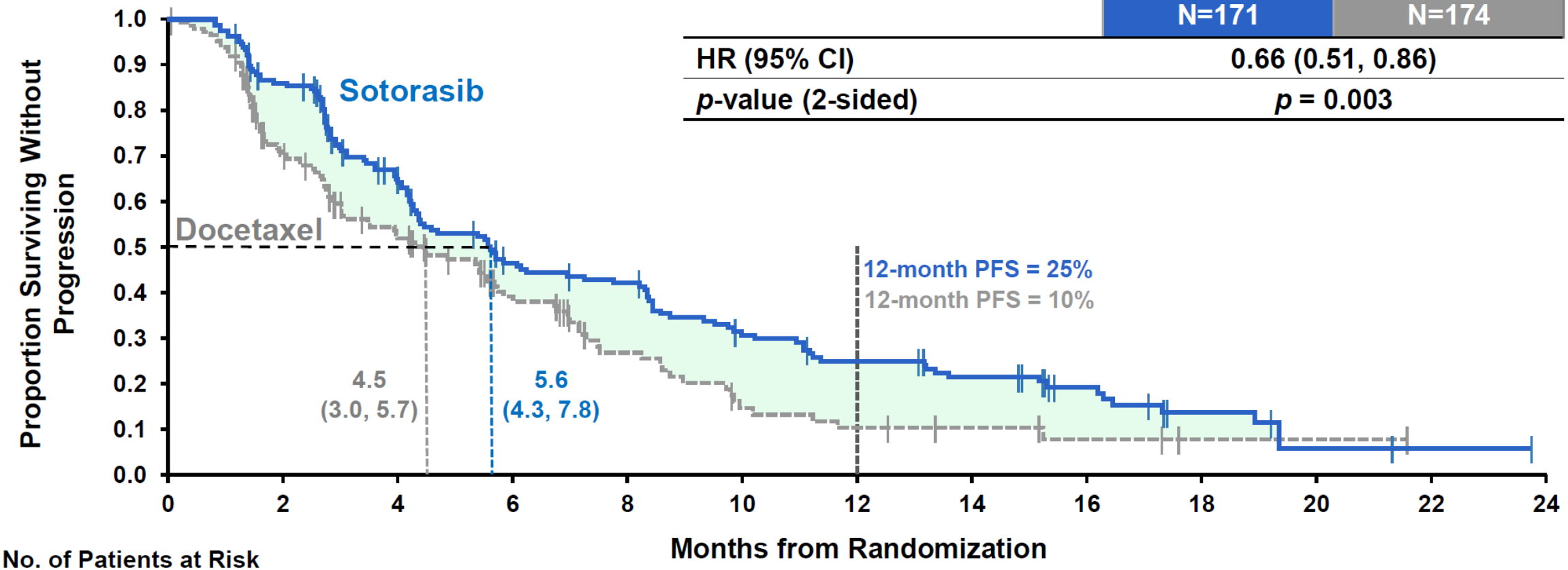
***Crossover implemented with Protocol Amendment 3, after 99% of patients had been enrolled.**

chemo: chemotherapy; CNS: central nervous system; DOR: duration of response;
IO: immuno-oncology therapy; OS – overall survival; PFS – progression-free survival; Q3W: every three weeks

Primary Endpoint Met – PFS by BICR

Sotorasib Reduces Risk of Progression or Death by 34%

	Sotorasib N=171	Docetaxel N=174
HR (95% CI)	0.66 (0.51, 0.86)	
p-value (2-sided)	*p* = 0.003	



No. of Patients at Risk

Sotorasib	171	139	93	63	56	38	30	24	14	6	2	1	0
Docetaxel	174	93	62	36	20	10	7	5	3	1	1	0	

Sotorasib demonstrated PFS, ORR and QoL improvement, but not OS

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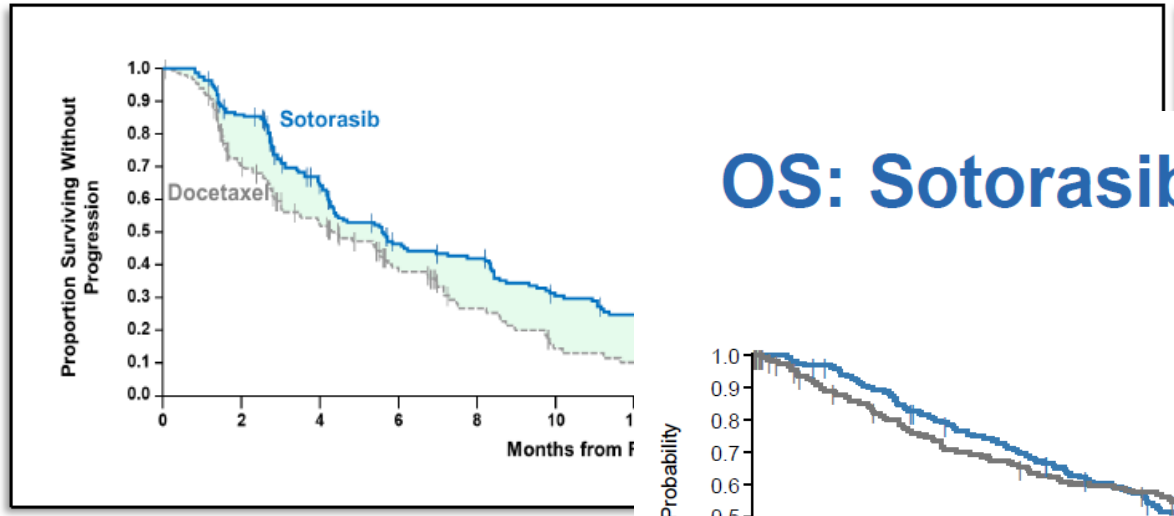
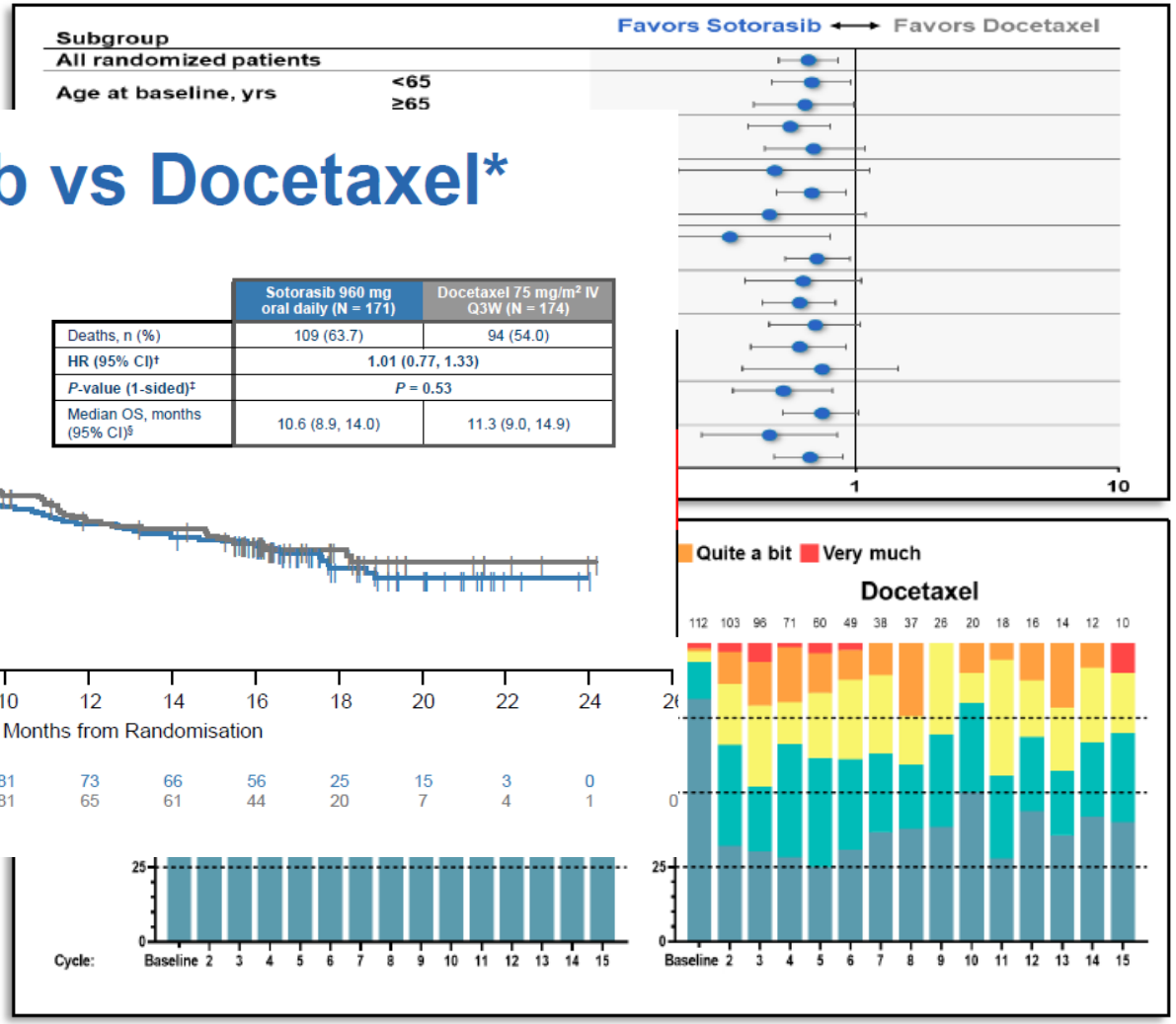
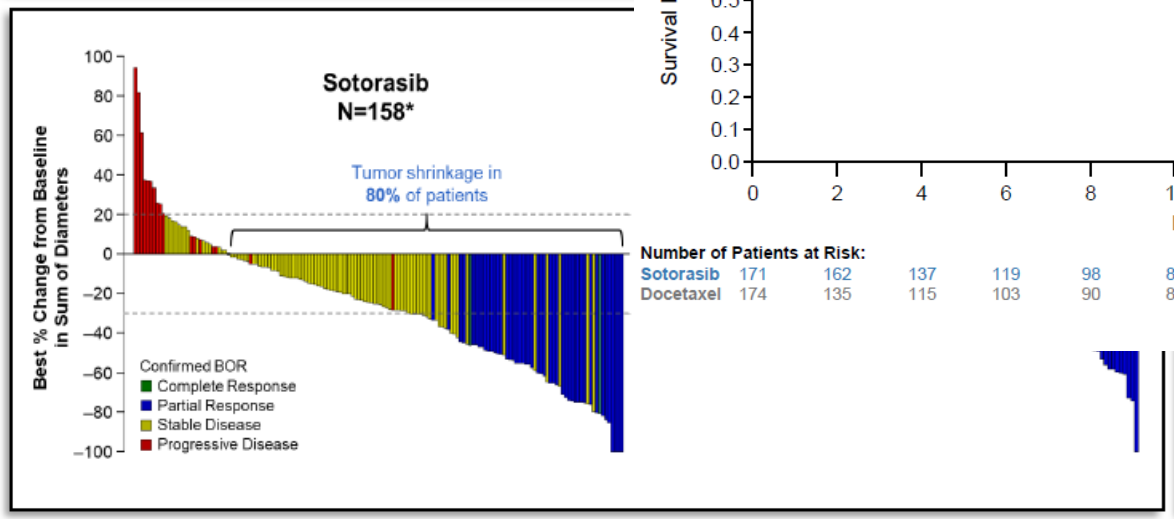




OS: Sotorasib vs Docetaxel*

	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
Deaths, n (%)	109 (63.7)	94 (54.0)
HR (95% CI)†	1.01 (0.77, 1.33)	
P-value (1-sided)‡	*P* = 0.53	
Median OS, months (95% CI)§	10.6 (8.9, 14.0)	11.3 (9.0, 14.9)



FACT-G GP5: "I am bothered by side effects of treatment"

CC-99

CodeBreaK 200 Study Design vs Study Conduct

Study Design Features:

- Open-label
- Randomization
- Stratification factors
- Sample size
- Endpoint selection
- Crossover

Study Conduct Issues:

- Potential violation of protocol and imaging charter
- Asymmetric patient dropout
- Investigator assessments favoring sotorasib arm
- Heterogeneity and potential bias in patient management (e.g., early crossover)
- Minimal OS follow-up for patients who dropped out

Mitigation Strategies

What is an Adequate and Well-Controlled (AWC) Trial?

- Clear statement of objectives and methods of analysis
- Design permits a valid comparison with a control
- **Adequate measures to minimize bias** in subject assignment to treatment group, to assure comparability of the groups
- **Adequate measures to minimize bias** on the part of subjects, observers, and analysts of the data
- Well-defined and **reliable methods to assess response**
- **Adequate analysis of the results of the study to assess the effect of the drug**

Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products *Guidance for Industry,* 2019
21 CFR 314.126

Mitigating Bias in Open-Label Trials: Lessons Learned

- Patient and investigator education
- Allowance of crossover
- Real-time BICR assessments
- Endpoint selection (PFS vs OS)
- Collection of OS follow-up even for patients who withdraw early

FDA Concerns regarding multiple signals of potential systemic bias and its effect on interpretation of Study result

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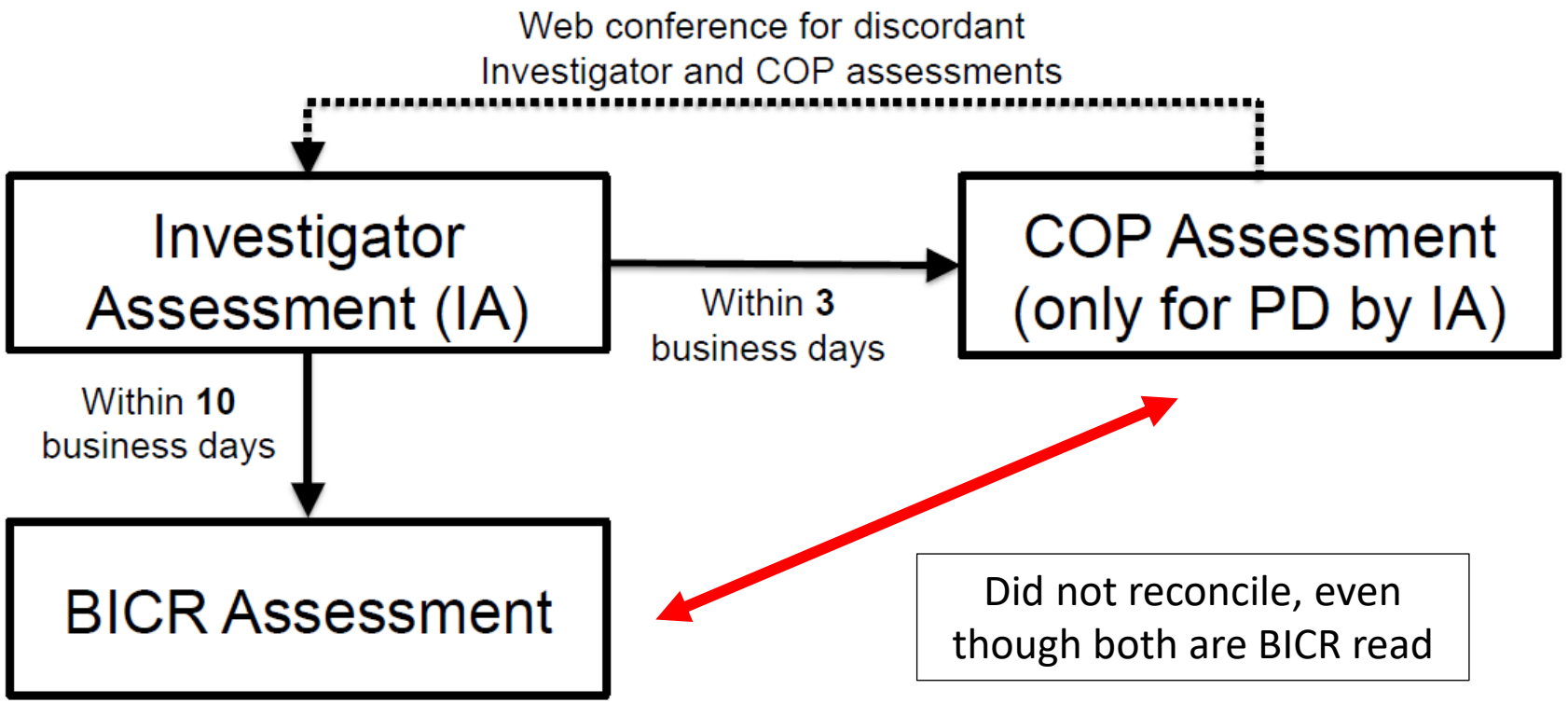
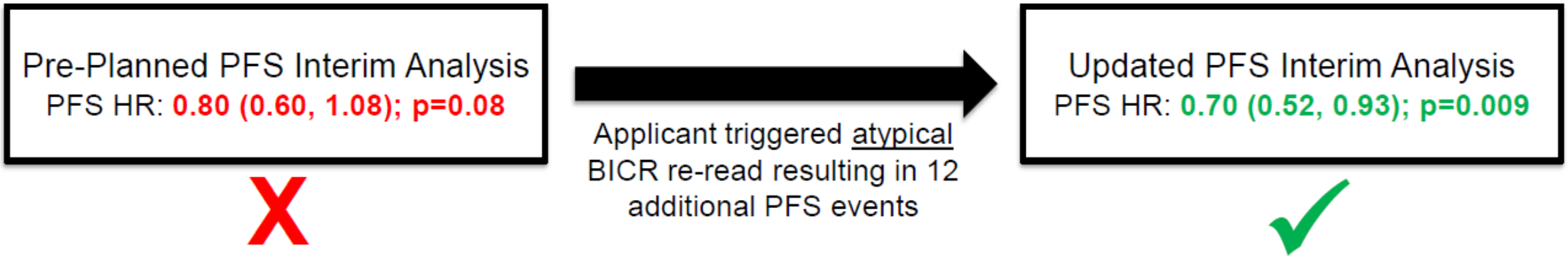
- **Asymmetric dropout** leading to potential loss of randomization
- **Investigator bias**, imaging assessments favoring sotorasib arm
- Applicant triggered radiologic **re-reads changing PFS interim results** (based on 12 additional PFS events)
- Perceived **loss of equipoise** in CodeBreak 200 may have led to potential systemic bias and study conduct issues
- **Systemic biases** are difficult to prove, but data may signal their presence
  - Asymmetric early dropout
  - Investigator imaging assessments favoring sotorasib arm
- Such biases can also permeate to other aspects of trial conduct
  - E.g., patient selection, adverse evet reporting, PROs

Confirmation of Progression (COP) Prior to Crossover or Treatment Beyond Progression



Potential impact of COP procedure usually minimal, if used as intended.

Potential Misuse of COP Procedure



- Applicant observed "higher than expected discrepancy" between COP- and BICR-based events of progression and "raised concerns" with imaging vendor, triggering BICR re-read.

- Per imaging charter, "Response assessments performed by [imaging vendor] are not subject to input from [Applicant], its designees, or any site involved in this clinical trial."

FDA considers this a potential violation of imaging charter.

Discordance in Assessment of Progressive Disease

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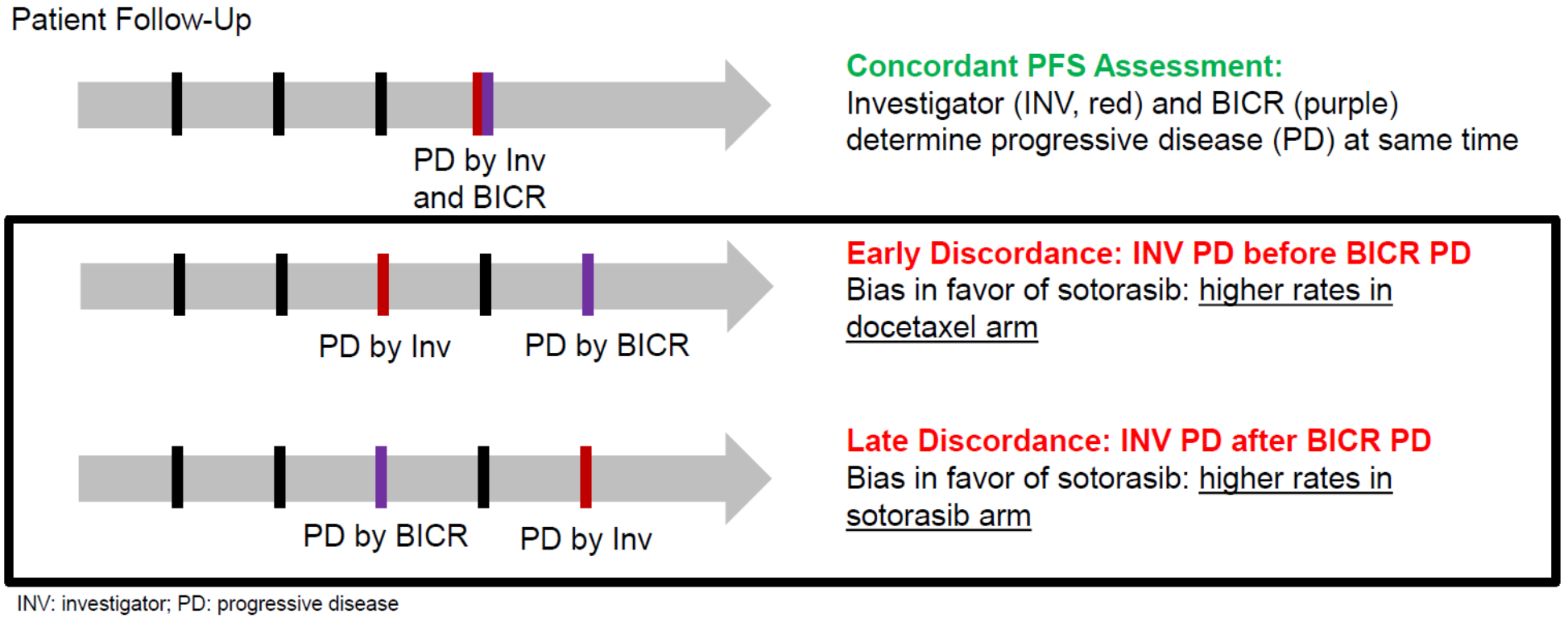
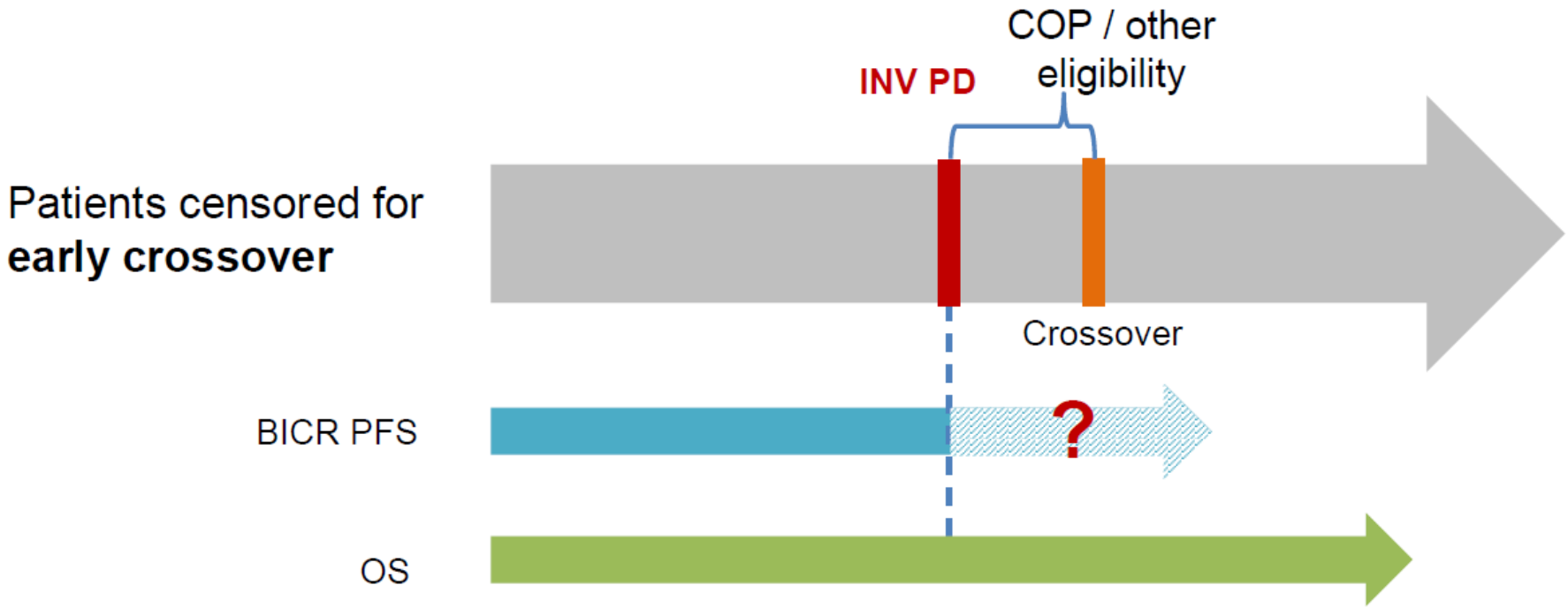


INV: investigator; PD: progressive disease

Potential Bias Favoring Sotorasib:

Differential distribution of early and late discordances among all discordances is suggestive of an investigator assessment bias

Early Calls by Investigators Compromised Integrity of Primary Endpoint



Potential informative censoring:

Crossover is based on investigator PD call, given COP and other eligibility criteria are met

FDA Analysis to Investigate PFS and OS in Crossover Patients

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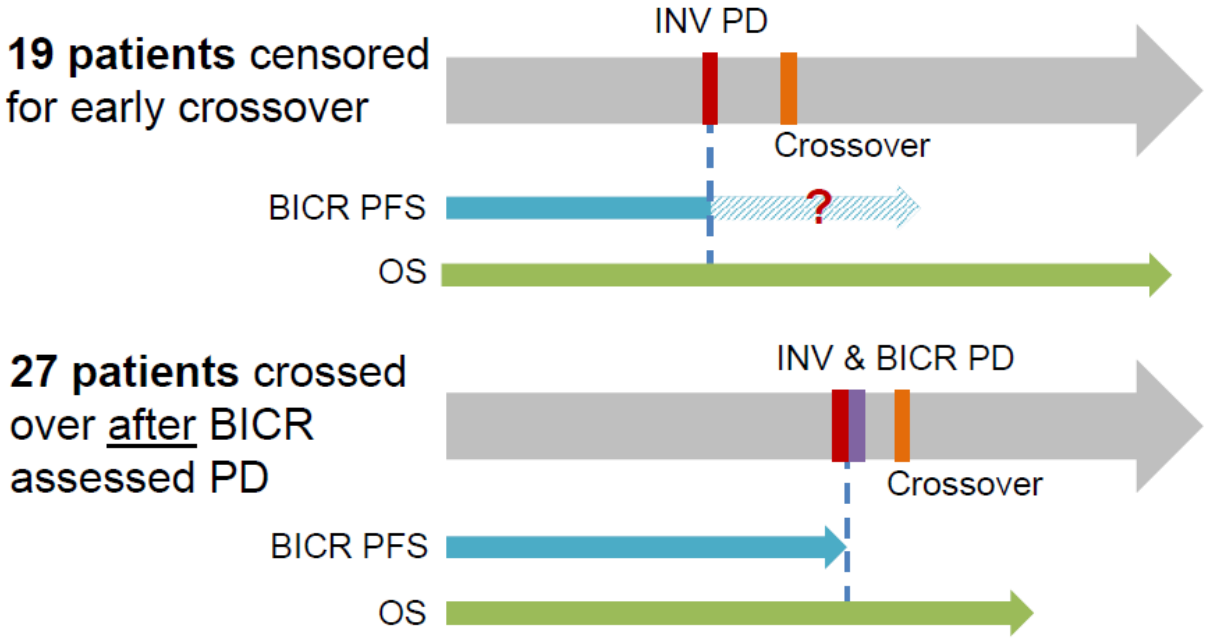

PFS Per BICR Assessment	Death Rate and Median OS post PD by INV
Censored at last BICR assessment prior to crossover	**47%** **18.9 months**
Event at BICR assessment of PD	**70%** **11.8 months**

Potential Bias Favoring Sotorasib:

Exploratory comparison of survival indicates that early crossover patients may be healthier than those who crossover after BICR assessed PD (HR of 0.42 with 95% CI: 0.19, 0.95)

Site Vs Central Reads

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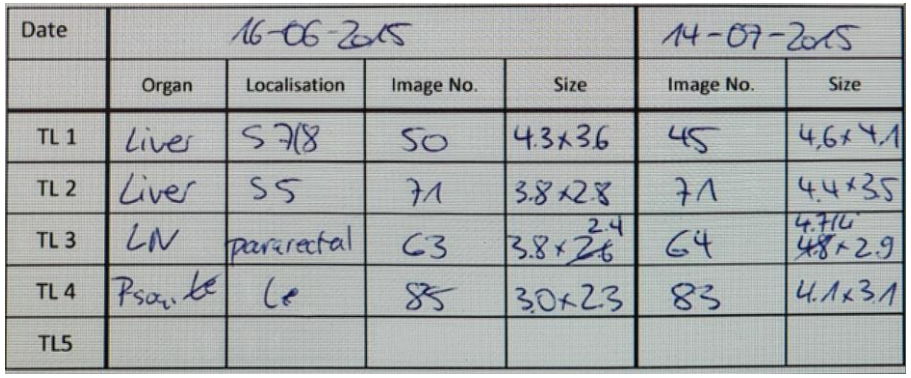
Central reads - Advantages

- Blinded reads with better application of assessment criteria
- Radiologists are better trained on criteria and how to review images in clinical trials
- Radiologists select and follow the disease burden more carefully
- Fewer radiologist readers leads to less variability in reads
- The same radiologist usually reviews the case for a given subject
- Better quality control and monitoring at CROs
- Not influenced by patient/ PI- No Bias;

Site reads - Disadvantages

- Site reads are biased by investigator
- Chance of variability as several readers may read the same case and multiple sites have multiple readers
- Radiologist training may vary across sites
- No dedicated software to do the reads in majority of sites



Date	16-06-2015				14-07-2015	
	Organ	Localisation	Image No.	Size	Image No.	Size
TL 1	Liver	S7/8	50	4.3x3.6	45	4.6x4.1
TL 2	Liver	S5	71	3.8x2.8	71	4.4x3.5
TL 3	LN	paraaortal	63	3.8x2.6 → 2.4	64	4.7/6 / 4.8x2.9
TL 4	Psoas	Le	85	3.0x2.3	83	4.1x3.1
TL5						

Multiple Signals of Potential Systemic Bias and Study Conduct Issues

- Applicant triggered radiologic re-reads changing PFS interim results (based on 12 additional PFS events)
- Asymmetric dropout leading to potential loss of randomization
- Investigator imaging assessments favoring sotorasib arm

FDA advised against submission of marketing application based on PFS interim analysis given concerns for integrity of PFS per BICR results

↓

Global BICR Re-Read

Imaging Vendor Procedures
Primary Analysis Based Upon 100% BICR Re-Read

- **PFS endpoint determined by BICR**
  - All study procedures adhered to protocol and imaging charter
- **Periodic event projections identified discordance**
  - Charter-directed quality review updated 11 progression events
  - Concern that quality review selectively influenced docetaxel arm
- **Mitigation implemented with 100% re-read by new and independent BICR team**

Primary analysis based on 100% re-read

Voting Question and results

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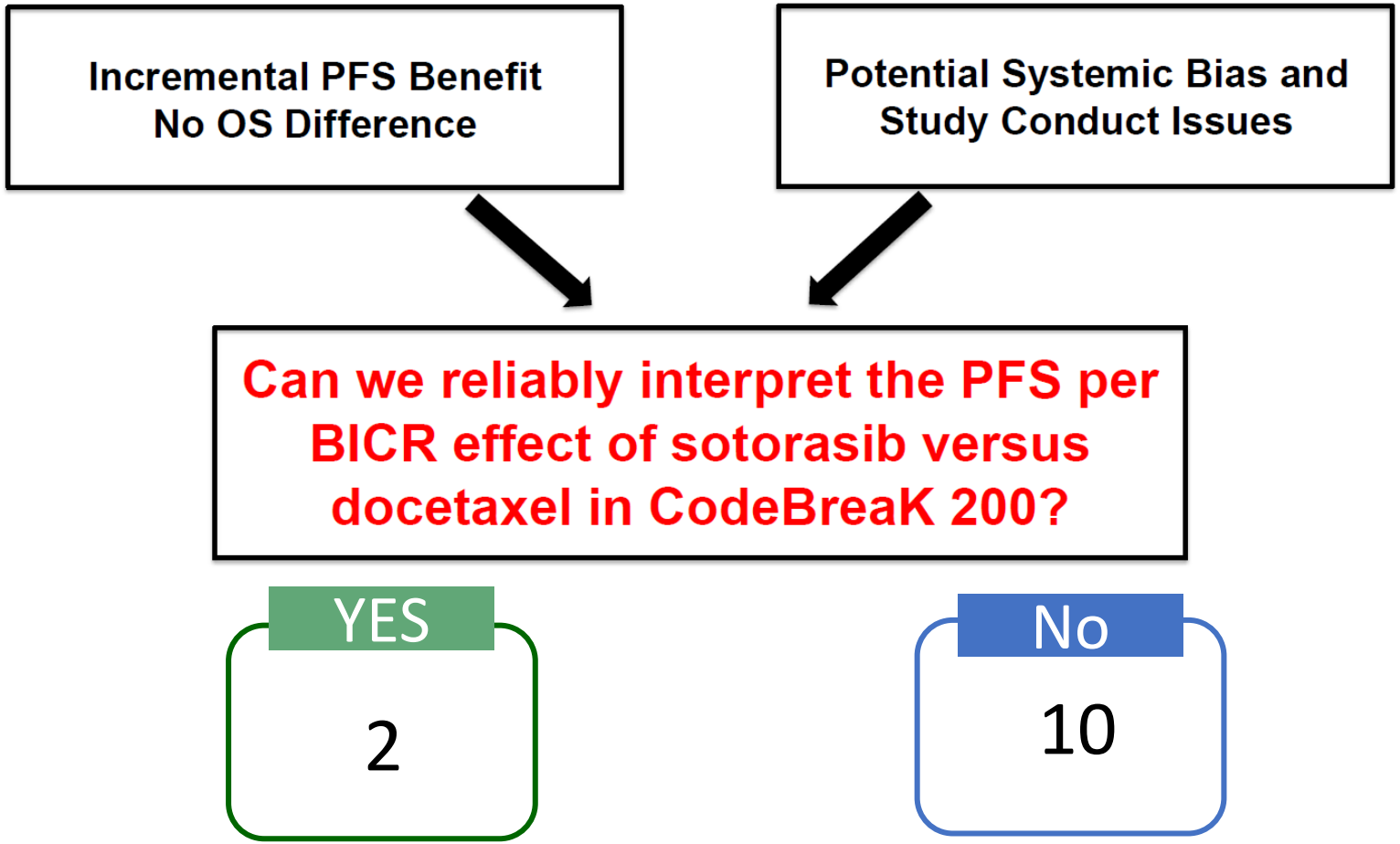
- Given multiple regulatory pathways and the evolving therapeutic landscape, FDA did not seek the advice of the committee as to whether CodeBReak 200 should be used to convert the accel. approval to full approval. Rather, they asked the committee to disucss the findings of CodeBreak 200, the multiple signals of potential bias, and if the PFS per BICR could be reliably interpreted



Comments from ODAC Advisory Committee

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"Yes"

Dr. Nieva (USC): "I voted yes because the study met its primary endpoint based on the intent-to-treat analysis, and ultimately we have to take the statistical plan as it is written and analyze things according to what was planned."

Dr. Shaw (Kaiser Permanente): "I feel strongly that there was a robust look at the data from both the FDA and also the sponsor. … I think for a rare disease setting, cancer setting, there was a large number of events for progression-free survival… even with many what-if scenarios for changing the results or imputing results for patients, we saw remarkably consistent effect."

"No"

Dr. Conaway (U of Virginia): "no one expects a perfect RCT. But what we hope for is a small number of issues in trial conduct, and an effect large enough to withstand the uncertainties caused by those issues. For this trial, we seem to have the opposite: a large number of issues that cloud the interpretation of a small observed effect."

Dr. Madan (NIH): "The factors that contribute to this are lack of certainty really come from again the small size investigator conduct and the small five-week PFS benefit. I do think if the PFS benefit was much greater, this would have been a much shorter conversation."

Dr. Rasko (OSU): "The process to me by which the radiologic re-read was performed and triggered a subsequent reanalysis impacted the integrity of the data of the study to me, and this opened up other questions about that immediate dropout, the crossover without bigger confirmed progression."

Key takeaways/lessons learned

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- **Imaging assessments are key in oncology trials and could make or break the trial if not managed properly.**

- **Manage biases in trial.**
  - **Study design**
  - **Open label vs blinded**
  - **Investigator assessments may be biased towards experimental drug – various reasons: BICR review**

- **It is important to be very careful with re-read reasons with BICR. Maintain integrity of the BICR read. Should not by any means appear as data manipulation.**

- **Crossover eligibility and design considerations (Crossover should have been based on BICR read?)**

Thank you!!

Panel Discussion

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Takeda Pharmaceutical Company Limited

Annette Schmid, PhD
Sr Director Global Science Policy
Takeda Pharmaceutical Company Limited

Gregory Goldmacher, MD, PhD, MBA
Associate VP, Global Clinical Trial Operations
Head of Clinical Imaging & Pathology
Merck

Questions for Panel discussion

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- How to design a trial with PFS as primary endpoint to avoid censoring bias (patient off study by PI decision versus central review)
  - Not to have 2 different BICR streams for confirmation of progression
- Some key best practices in managing a BICR read- Do’s for BICRs and Don'ts for Sponsor
- What would have you done different for this trial
- *Site central discordance- When to worry, how to reduce it?*
- *BICR versus Investigator read in registrational trials especially open label.*