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

Oncologic Drugs Advisory Committee Meeting
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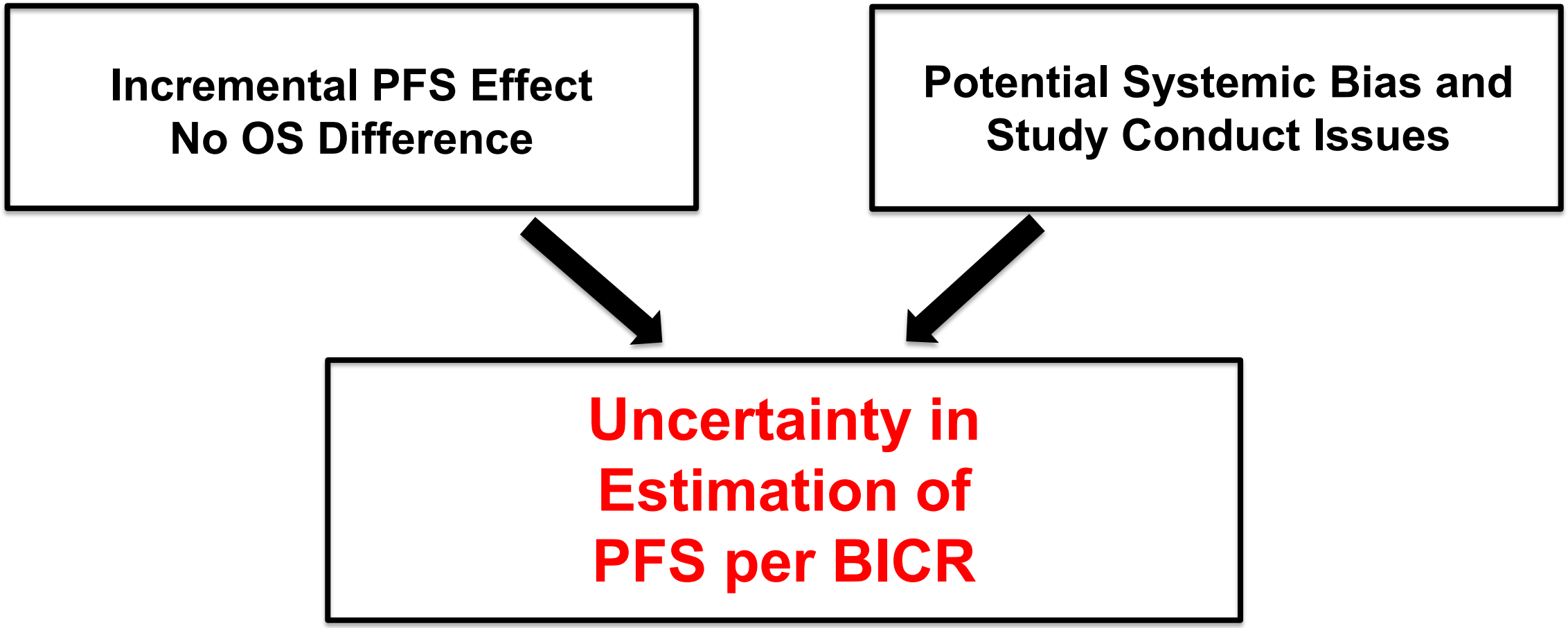
CodeBreaK 200



BICR: blinded independent central review; PFS: progression-free survival; OS: overall survival

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

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

Can we reliably interpret the primary endpoint, PFS per BICR, in CodeBreaK 200?

Sotorasib in the Press

“Amgen unveils its first Kras inhibitor in clinical trials: AMG 510 shuts down a mutant version of the cancer target via covalent interaction”
Chemical & Engineering News – Drug Discovery, April 3, 2019

“ASCO 2019 – KRAS Chase Heats up with Amgen Data”
Evaluate Vantage, June 4, 2019

“FDA Grants AMG 510 Fast Track Designation for KRAS G12C+ NSCLC”
Targeted Oncology, September 9, 2019

“The Discovery of Amgen’s Novel Investigational KRAS(G12C) Inhibitor AMG 510 Published in Nature”
Cision PR Newswire, October 30, 2019

“AMG 510 Shows Clinical Activity in Advanced KRAS G12C-Mutant Solid Tumors”
OncLive, May 30, 2020

“Amgen’s Investigational KRAS G12C Inhibitor Sotorasib Demonstrated Rapid, Deep and Durable Responses in Previously Treated Patients With Advanced Non-Small Cell Lung Cancer”
Amgen Press Release, January 28, 2021

Perceived Loss of Equipoise

- Loss of equipoise occurs when there is certainty that one intervention is better than the other
  - Equipoise considered necessary for the ethical conduct of a randomized trial

- *Perceived* loss of equipoise is the belief that one intervention is better, even without definitive evidence
  - Behaviors may change, especially in setting of open-label design

Perceived loss of equipoise in CodeBreaK 200 may have led to potential systemic bias and study conduct issues

The Belmont Report: ethical principles and guidelines for the protection of human subjects and research, 1979.

CodeBreaK 100: Accelerated Approval

Accelerated approvals require:

- *Substantial evidence of effectiveness*
- *Endpoint reasonably likely to predict clinical benefit*
- *Meaningful therapeutic benefit over available therapy*

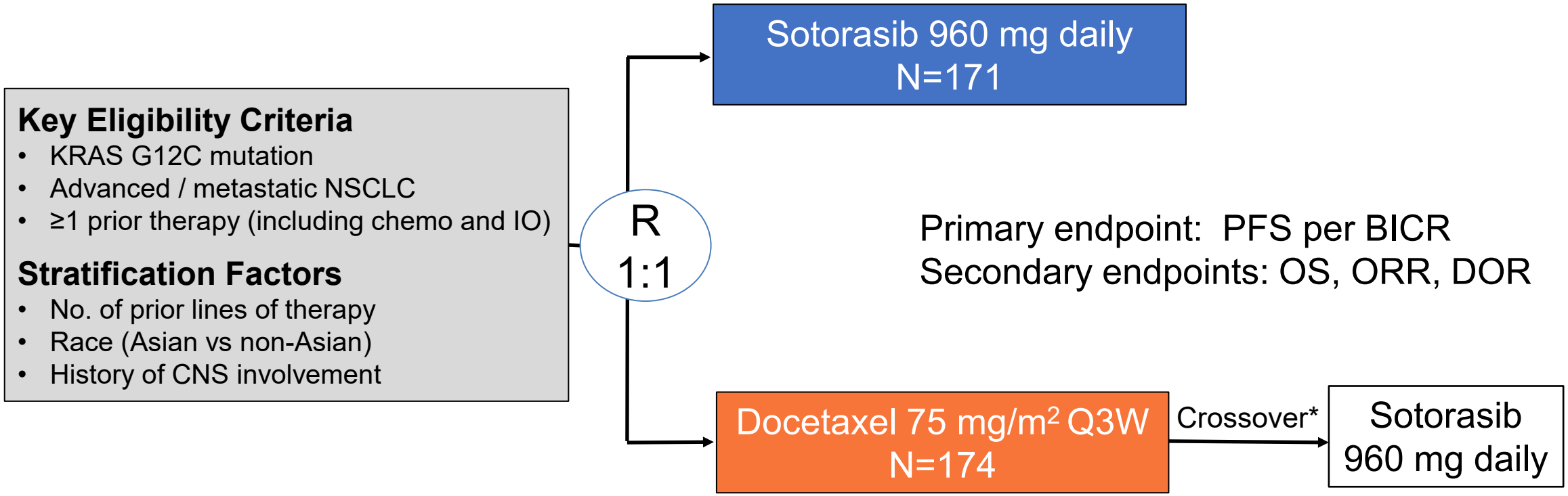
CodeBreaK 100	Sotorasib 960 mg daily KRAS G12C NSCLC N = 124
ORR per BICR, % (95% CI)	**36 (28, 45)**
Median duration of response, mos (95% CI)	**10.0 (6.9, NE)**

Available therapy: Docetaxel ORR – 8-12%

CI: confidence interval; N: number; NE: not evaluable; NSCLC: non-small cell lung cancer; ORR: objective response rate

21 CFR Part 314, Subpart H; 21 CFR Part 601, Subpart E
LUMAKRAS (sotorasib) USPI
KEYTRUDA (pembrolizumab) USPI
OPDIVO (nivolumab) USPI

CodeBreaK 200: Open-label Trial Design



***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; Q3W: every three weeks

Progression-Free Survival

- Commonly accepted as a primary endpoint in oncology trials
- Based on subjective interpretation of radiographic images
  - Variability in timing of assessments
  - Intra- and inter-reader variability
- FDA conducts sensitivity analyses to explore strength of primary PFS analysis
  - Magnitude of benefit should withstand sensitivity analyses

Singh and Pazdur, JAMA Oncol, 2021
FDA Guidance to Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics, 2015

CodeBreaK 200: Topline Efficacy Results

	Sotorasib N = 171	Docetaxel N = 174
Median PFS per BICR, months (95% CI)	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)
PFS events, n (%)	122 (71)	101 (58)
HR (95% CI)	0.66 (0.51, 0.86)	
p-value	0.002	
Median OS, months (95% CI)	10.6 (8.9, 14.0)	11.3, (9.0, 14.9)
Deaths, n (%)	109 (64)	94 (54)
HR (95% CI)	1.01 (0.77, 1.33)	
p-value	0.53	
ORR per BICR, % (95% CI)*	28 (22, 35)	13 (9, 19)
Crossover from Docetaxel to Sotorasib, n (%)	---	46 (26%)

* P-value <0.001
HR: hazard ratio
Primary analysis data cutoff date: August 2, 2022
Source: FDA review based on datasets submitted in NDA 214665 s005

Early Withdrawal of Patients on Docetaxel Arm

Disposition in CodeBreaK 200	Sotorasib, 960 mg N = 171 n (%)	Docetaxel N = 174 n (%)
Patients randomized but not dosed	**2 (1.2)**	**23 (13)**
Patient request / withdrawal of consent	1 (0.6)	20 (11)
Adverse event	1 (0.6)	0
PI decision	0	1 (0.6)
Disease progression	0	1 (0.6)
Lost to follow-up	0	1 (0.6)
Patients who received at least one dose	**169 (99)**	**151 (87)**

PI: primary investigator
Primary analysis data cutoff date: August 2, 2022
Source: FDA review based on datasets submitted in NDA 214665 s005

Asymmetric dropout concerning for investigator and patient preference for sotorasib

Open-label Trials: Potential Systemic Bias

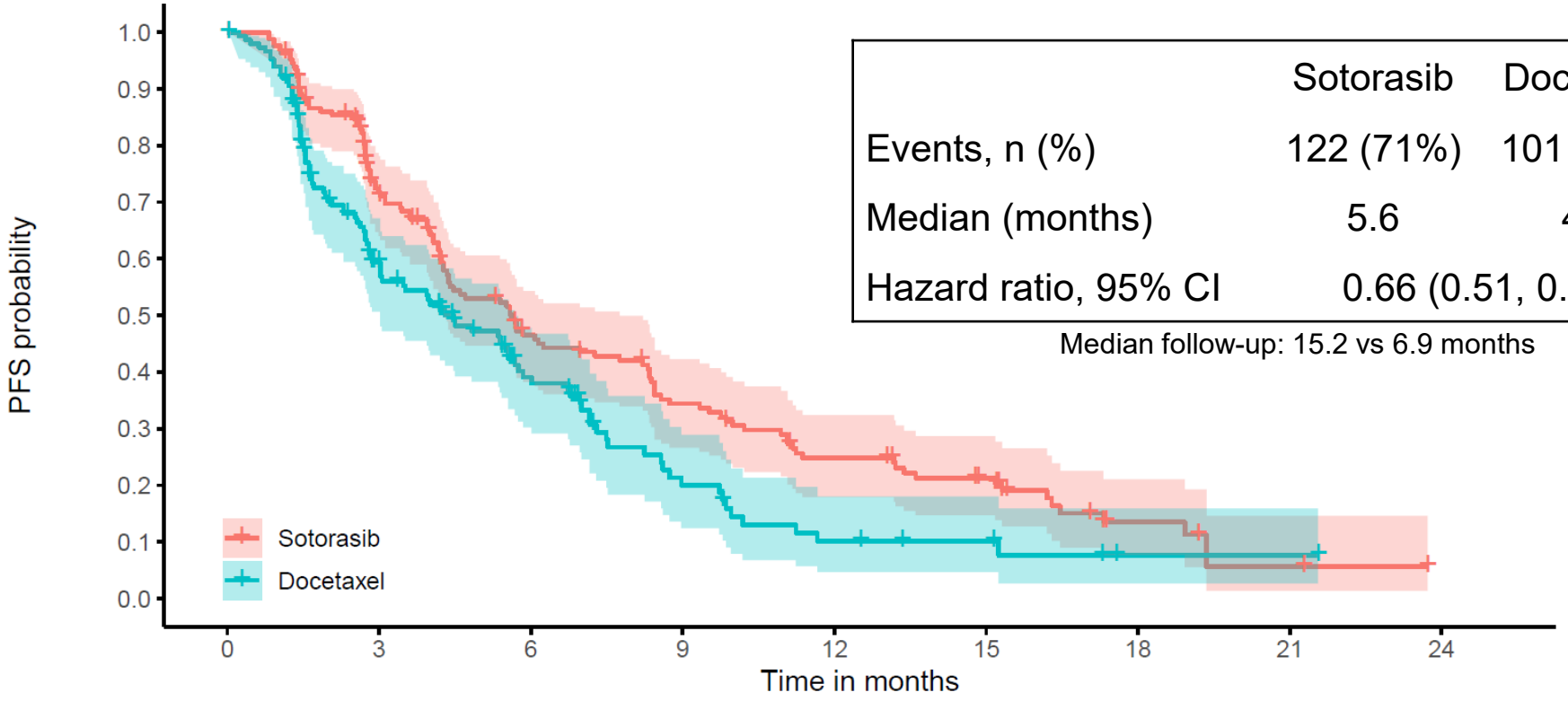
- Open-label trials are susceptible to bias, particularly when the control treatment is known to perform poorly
  - Docetaxel control arm with historical ORR of 8 -12%
- Systemic biases are difficult to prove, but data may signal their presence
  - Asymmetric early dropout
  - Investigator imaging assessments favoring sotorasib arm
- Such biases can also permeate to other aspects of trial conduct
  - Examples: patient selection, adverse event reporting, and PROs

PROs: patient reported outcomes

KEYTRUDA (pembrolizumab) USPI
OPDIVO (nivolumab) USPI

FDA Analyses: Efficacy and Safety

FDA Analysis: PFS per BICR



	Sotorasib	Docetaxel
Events, n (%)	122 (71%)	101 (58%)
Median (months)	5.6	4.5
Hazard ratio, 95% CI	0.66 (0.51, 0.86)	

Median follow-up: 15.2 vs 6.9 months

Number at risk (cumulative number censored)

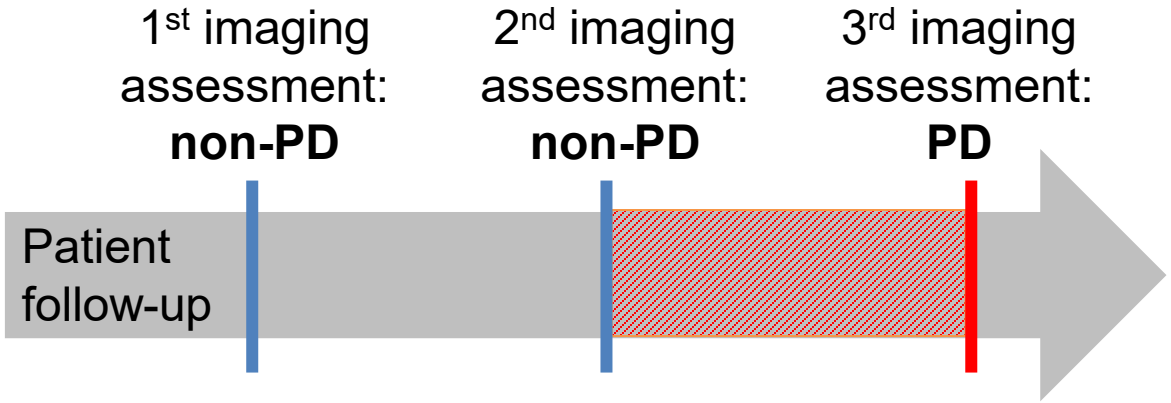
	0	3	6	9	12	15	18	21	24
Sotorasib	171 (0)	107 (19)	63 (27)	45 (29)	30 (32)	22 (36)	6 (46)	2 (47)	0 (49)
Docetaxel	174 (0)	71 (47)	36 (60)	15 (66)	7 (67)	5 (69)	1 (72)	1 (72)	0 (73)

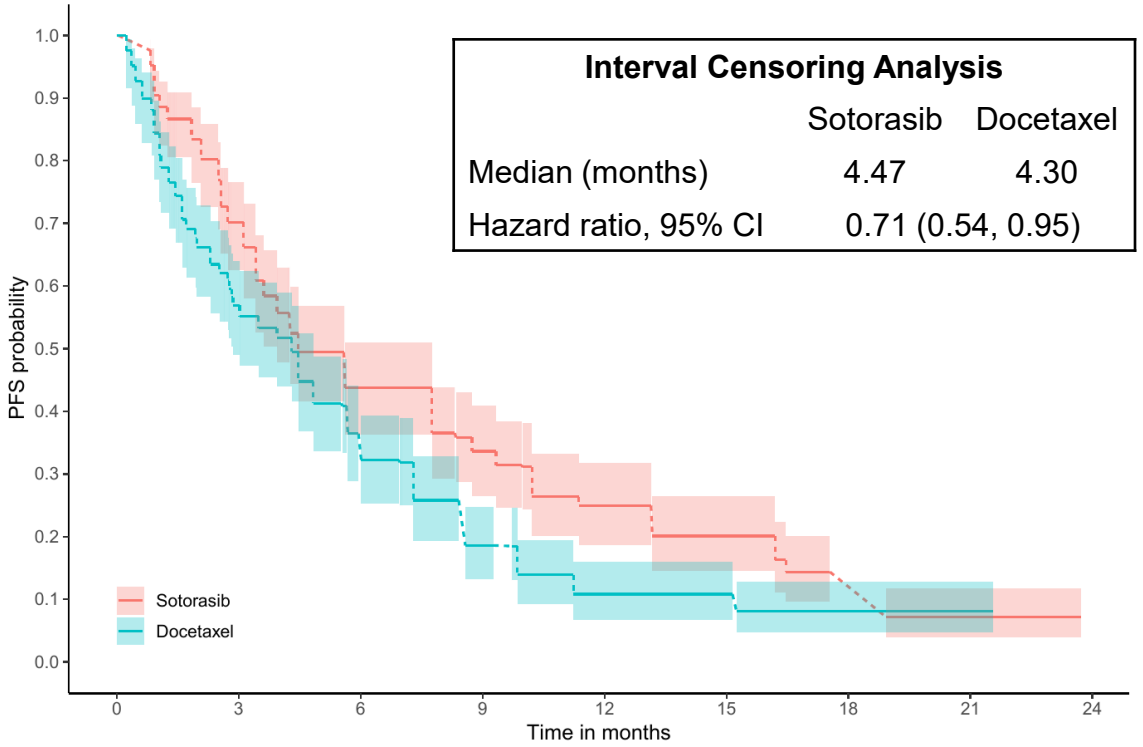
Time in months

Data cutoff date: August 2, 2022

Incremental PFS effect: 5 weeks relative to 6-week imaging interval

Impact of PFS Benefit Less than Imaging Interval





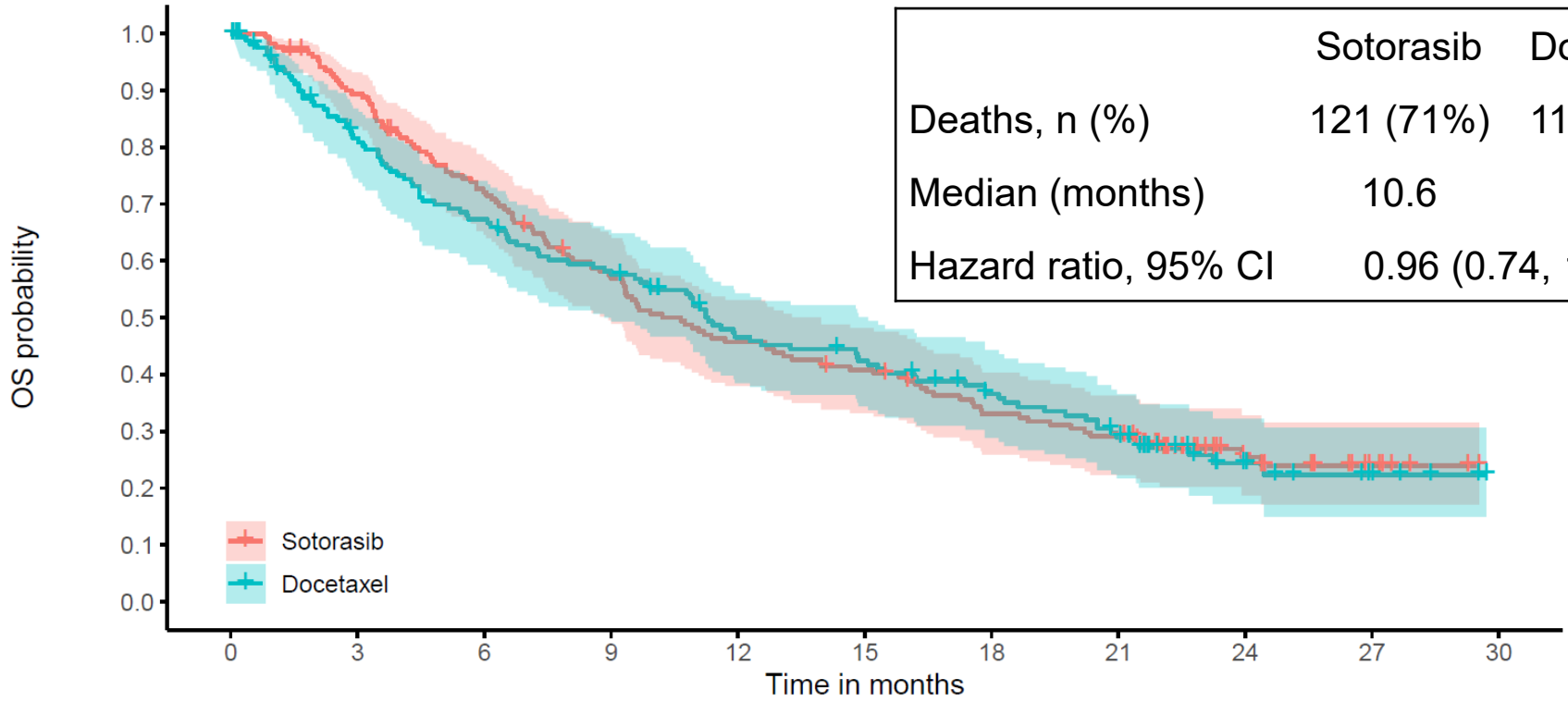
Interval Censoring Analysis

	Sotorasib	Docetaxel
Median (months)	4.47	4.30
Hazard ratio, 95% CI	0.71 (0.54, 0.95)	

Although the hazard ratio is relatively consistent, median PFS difference could be as small as **5 days**

FDA Analysis: Overall Survival

	Sotorasib	Docetaxel
Deaths, n (%)	121 (71%)	111 (64%)
Median (months)	10.6	11.3
Hazard ratio, 95% CI	0.96 (0.74, 1.24)	



Number at risk (cumulative number censored)

Sotorasib	171 (0)	151 (2)	120 (4)	93 (7)	74 (7)	65 (8)	51 (10)	45 (10)	17 (34)	6 (44)	0 (50)
Docetaxel	174 (0)	126 (19)	104 (19)	89 (20)	67 (25)	60 (26)	48 (30)	37 (31)	13 (51)	6 (57)	0 (63)

0 3 6 9 12 15 18 21 24 27 30

Time in months

Data cutoff date: January 18, 2023

Overall Survival not likely impacted by crossover

CodeBreaK 200: Summary of Safety

	Sotorasib, 960 mg daily N = 169 n (%)	Docetaxel 75 mg/m^2 Q3W N = 151 n (%)
All-cause TEAEs Any grade Grade ≥3	 138 (82) 94 (56)	 139 (92) 84 (56)
Fatal TEAEs	11 (7)	11 (7)
Serious TEAEs	64 (38)	60 (40)
TEAEs leading to discontinuation TEAEs leading to dose reduction TEAEs leading to dose interruption	22 (13) 26 (15) 83 (49)	22 (15) 42 (28) 40 (26)

TEAEs: treatment-emergent adverse events
Primary analysis data cutoff date: August 2, 2022
Source: FDA review based on datasets submitted in NDA 214665 s005

- **Overall, no new safety signals were identified for sotorasib in CodeBreaK 200**
- **Similar death rates in the safety population**

CodeBreaK 200: Patient Reported Outcomes

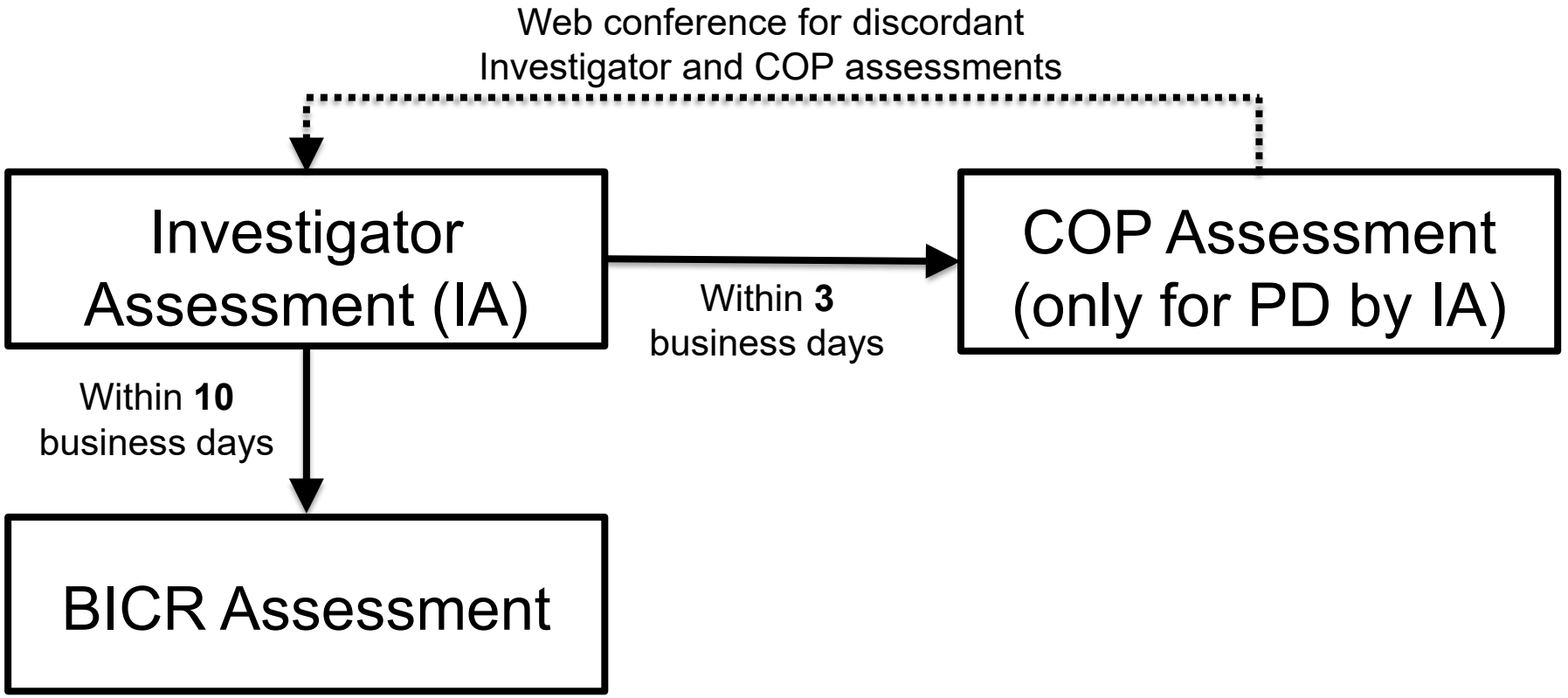
- High rates of PRO instrument completion for patients still on treatment
  - Does not account for asymmetric dropout

- Signal of higher side effect bother for patients on docetaxel arm supported by toxicity profiles

Systemic bias interferes with interpretation of all endpoints, particularly those with subjectivity in measurement, such as PROs

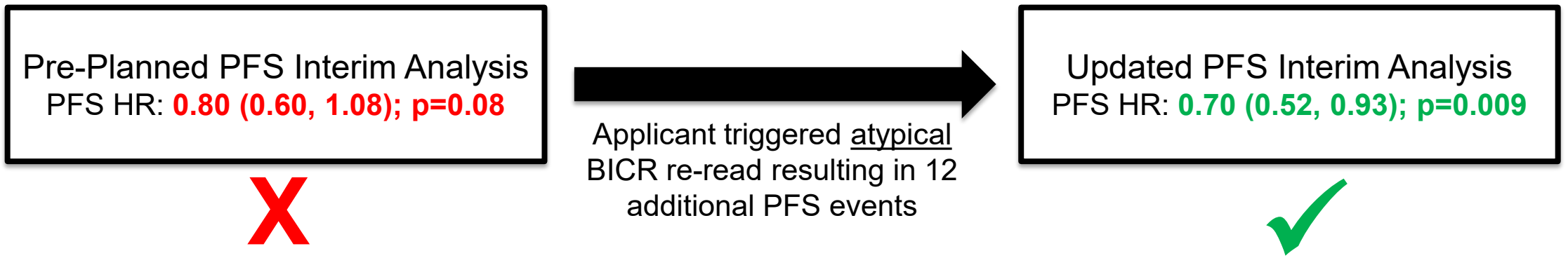
FDA Analyses: Study Conduct and Potential Systemic Bias

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.

Concerns Regarding Fidelity of PFS Endpoint

- Potential misuse of COP procedure to informally audit BICR
  - Potential study conduct issue
- Highlights intra- and inter-reader variability of PFS assessments

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

CodeBreaK 200: Potential for Systemic Bias

- Systemic biases are difficult to prove, but data may signal their presence
  - Signal #1: Asymmetric early dropouts between treatment arms
  - Signal #2: Investigator imaging assessments favoring sotorasib arm
  - Signal #3: Early crossover per investigator assessment affecting BICR assessments

CodeBreaK 200: Potential for Systemic Bias

- Systemic biases are difficult to prove, but data may signal their presence
  - Signal #1: Asymmetric early dropouts between treatment arms

Asymmetric Early Dropout of Patients Who Never Initiated Study Therapy

	Sotorasib N=171	Docetaxel N=174
Patients Not Treated	**2 (1%)**	**23 (13%)**

Statistical concern: Most of the 23 patients from control arm withdrew consent and censored at day 1 for not having post-baseline assessment

Potential Loss of Randomization

Asymmetric Early Dropout May Lead to Loss of Randomization and Bias

Potential loss of randomization:

- Known and unknown factors are generally balanced by randomization
- Balance can be lost if dropouts are predominantly on one arm
- Patients remaining on trial no longer directly comparable, resulting in biased estimation

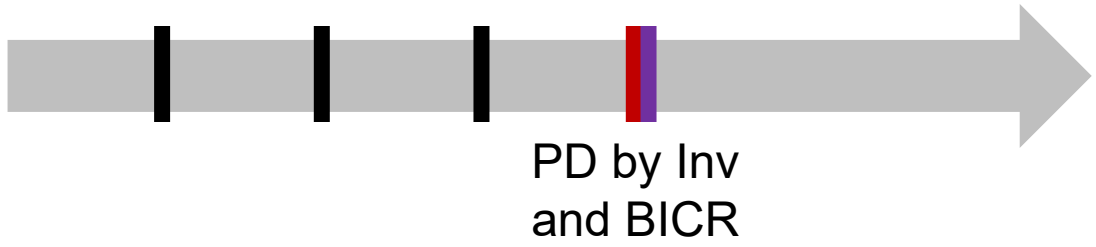
Potential Bias Favoring Sotorasib:
Censoring drop-out patients leads to **overestimation** of PFS treatment effect if these patients (mostly on docetaxel arm) would have had better outcomes.

CodeBreaK 200: Potential for Systemic Bias

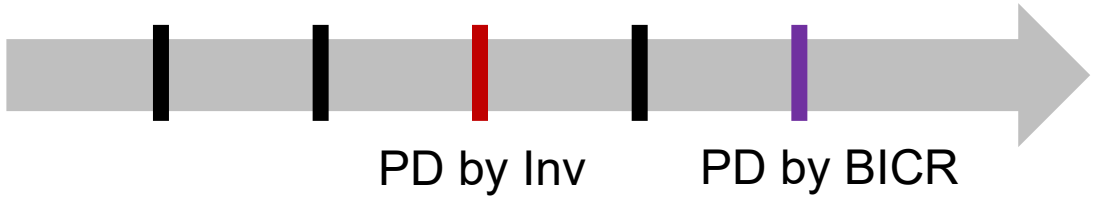
- Systemic biases are difficult to prove, but data may signal their presence
  - Signal #1: Asymmetric early dropouts between treatment arms
  - Signal #2: Investigator imaging assessments favoring sotorasib arm

Discordance in Assessment of Progressive Disease

Patient Follow-Up



Concordant PFS Assessment:
Investigator (INV, red) and BICR (purple) determine progressive disease (PD) at same time



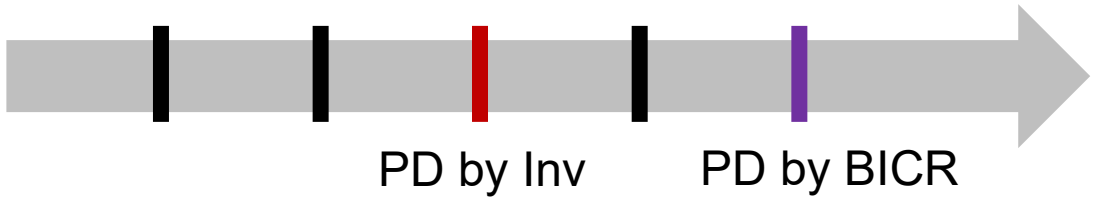
Early Discordance: INV PD before BICR PD
Bias in favor of sotorasib: higher rates in docetaxel arm

Late Discordance: INV PD after BICR PD
Bias in favor of sotorasib: higher rates in sotorasib arm

INV: investigator; PD: progressive disease

Discordance in Assessment of Progressive Disease

While some discordance is expected and observed in every trial, a **differential distribution of discordance** across arms may signal systemic bias

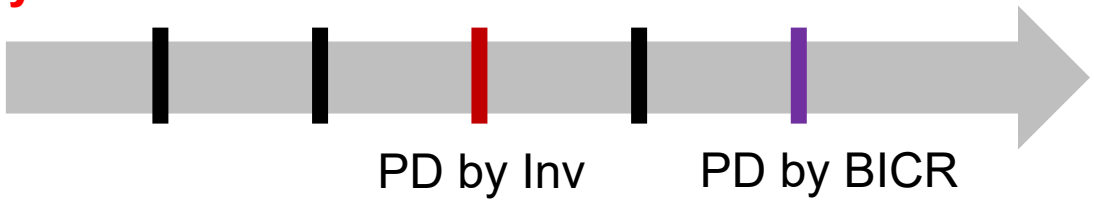


Early Discordance: INV PD before BICR PD
Bias in favor of sotorasib: higher rates in docetaxel arm

Late Discordance: INV PD after BICR PD
Bias in favor of sotorasib: higher rates in sotorasib arm

Differential Distribution of Discordances Across Arms

Early Discordance:



Late Discordance:

Discordant PDs (per INV and BICR timing)		
Sotorasib n = 89	vs	Docetaxel n = 67
52 (58%)	vs	**46 (69%)**
37 (42%)	vs	21 (31%)

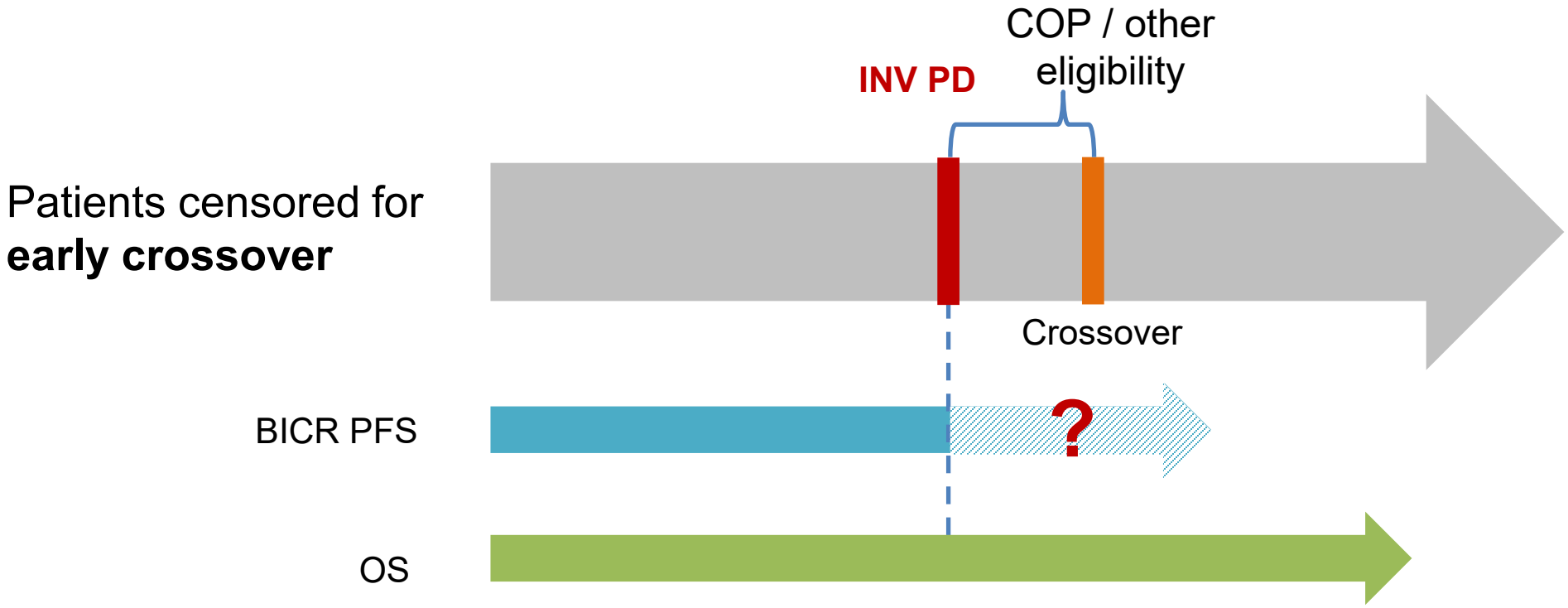
Potential Bias Favoring Sotorasib:

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

CodeBreaK 200: Potential for Systemic Bias

- Systemic biases are difficult to prove, but data may signal their presence
  - Signal #1: Asymmetric early dropouts between treatment arms
  - Signal #2: Investigator imaging assessments favoring sotorasib arm
  - Signal #3: Early crossover per investigator assessment affecting BICR assessments

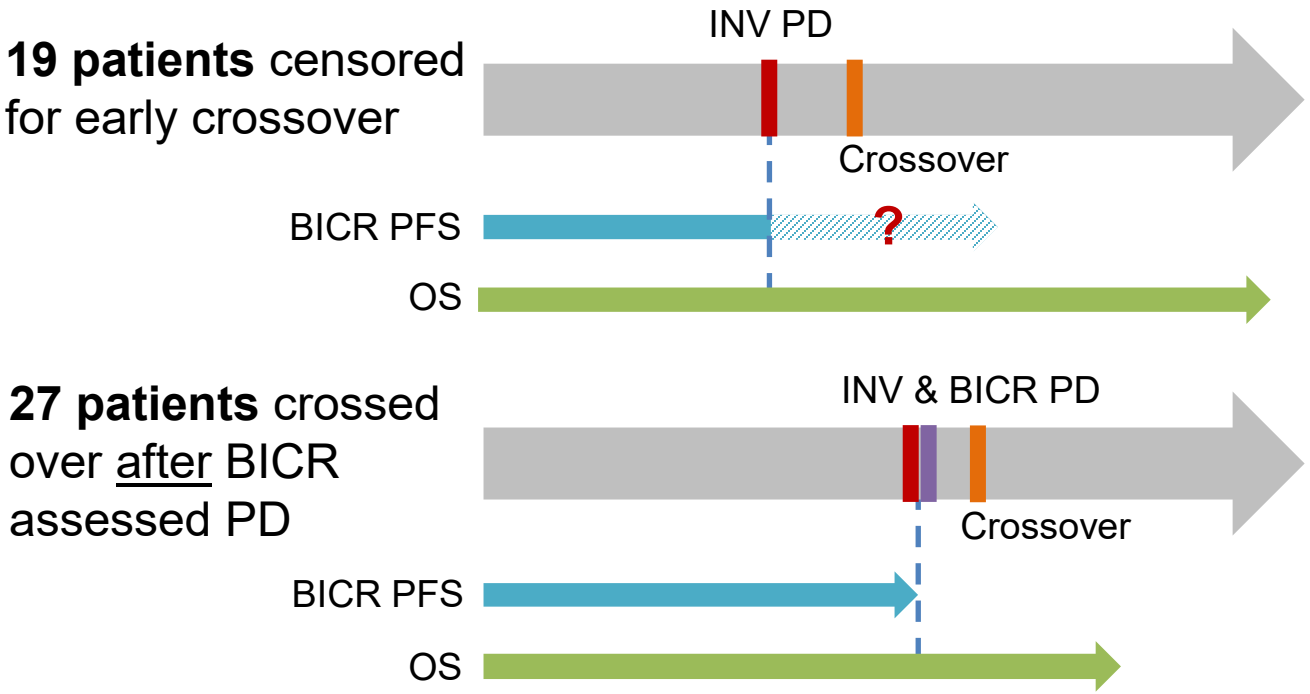
Early Calls by Investigators Compromised Integrity of Primary Endpoint



Potential informative censoring:

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

Patients Censored Due to Early Crossover may have had a Better Prognosis



	PFS Per BICR Assessment	Death Rate and Median OS post PD by INV
19 patients censored for early crossover	**Censored** at last BICR assessment prior to crossover	**47%** **18.9 months**
27 patients crossed over after BICR assessed PD	**Event** at BICR assessment of PD	**70%** **11.8 months**

Potential Bias Favoring Sotorasib:

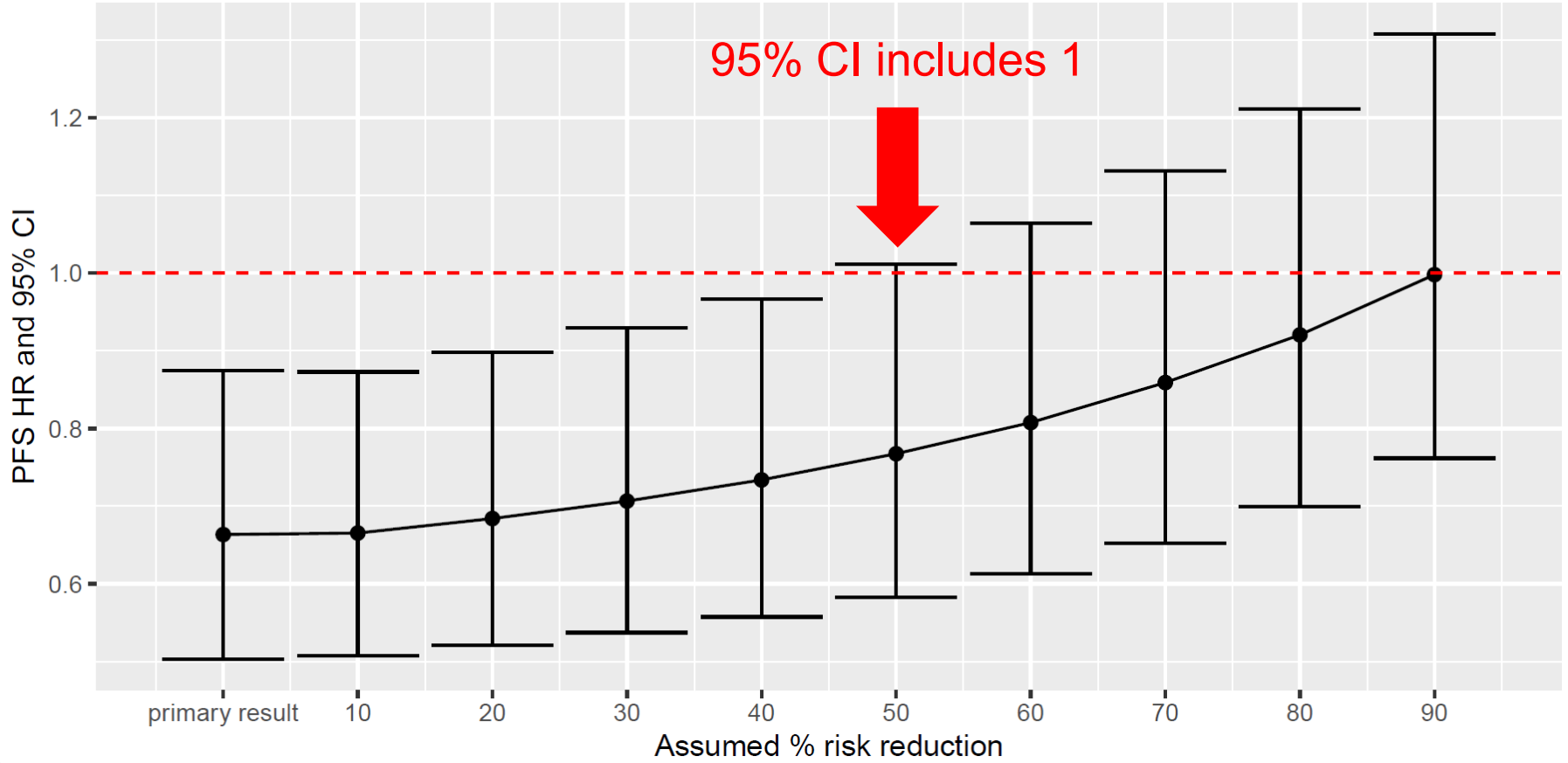
Exploratory comparison of survival indicates that early crossover patients may be healthier than those who crossover after BICR assessed PD (HR of 0.42 with 95% CI: 0.19, 0.95)

Assessing the Impact of Early Dropout and Early Crossover

- Asymmetric early dropouts
  - 20 patients in docetaxel arm withdrew consent within 5 weeks and censored due to no post-baseline assessment
- Patients with early crossover
  - 19 patients in docetaxel arm who crossed-over before BICR confirmation (with investigator PD only)

Sensitivity analyses: What if these patients are healthier than other patients in the docetaxel arm?

Potential Loss of Statistical Significance of PFS Endpoint



HR is no longer “statistically significant” if patients who dropped out or crossed over early are at 50% lower risk of PD than those remaining in follow-up

PD: disease progression or death

No Change in OS Results After Adjusting for Crossover

Analysis	HR (95% CI)
Primary analysis per protocol	1.01 (0.77, 1.33)
90-Day safety update	0.96 (0.74, 1.24)
RPSFTM adjusted analysis	0.96 (0.71, 1.43)
IPCW adjusted analysis	1.03 (0.78, 1.37)
Two-stage model	0.95 (0.63, 1.33)

Crossover is unlikely the reason for the observed lack of OS difference between sotorasib and docetaxel arms

RPSFTM: Rank Preserving Structural Failure Time Model IPCW: Inverse-Probability-of-Censoring Weighting

CodeBreaK 200 Results Difficult to Interpret Due to Systemic Bias

- There are several signals indicating presence of systemic bias which complicates reliable interpretation of the trial results
- These signals are more concerning due to incremental PFS benefit and no difference in OS
- The tipping point analysis suggests PFS may not remain "statistically significant" if there is moderate violation of the analysis assumption

Summary and Voting Question

CodeBreaK 200

Incremental PFS Benefit
No OS Difference

Potential Systemic Bias and Study Conduct Issues

Can we reliably interpret the PFS per BICR effect of sotorasib versus docetaxel in CodeBreaK 200?

PFS Endpoint in CodeBreaK 200

- Based on subjective interpretation of radiographic images
  - Intra- and inter-reader variability in CodeBreaK 200

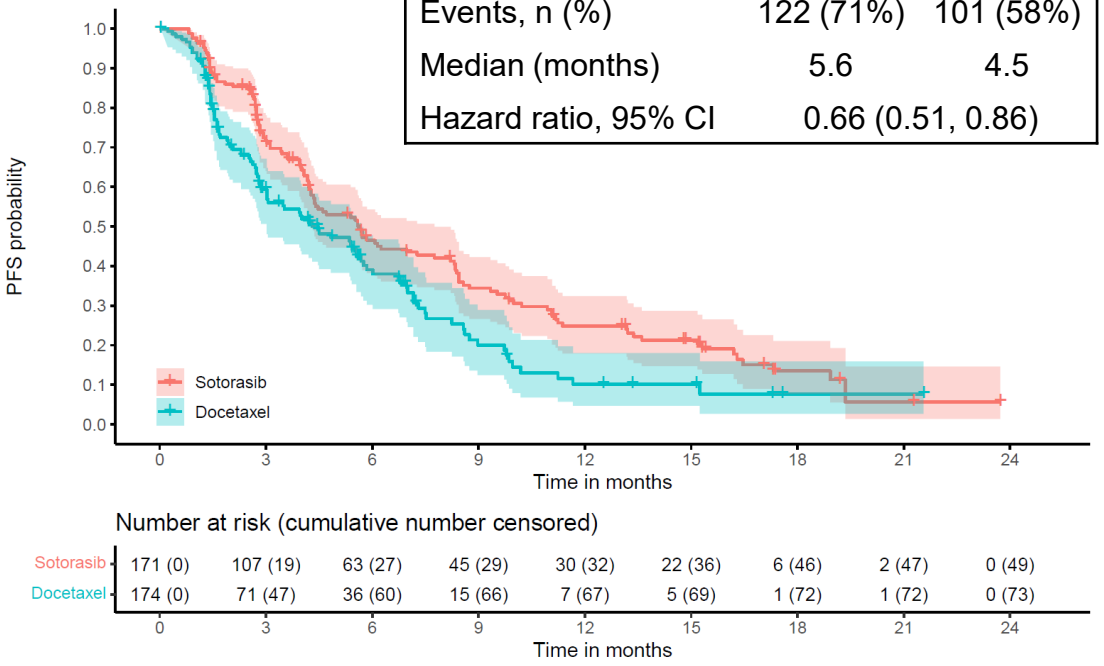
- FDA conducts sensitivity analyses to explore strength of primary analysis
  - Magnitude of benefit should withstand sensitivity analyses, but may not be the case for CodeBreaK 200 (tipping point analysis)

FDA Guidance to Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics, 2015

CodeBreaK 200: Top Line Results

Progression-Free Survival

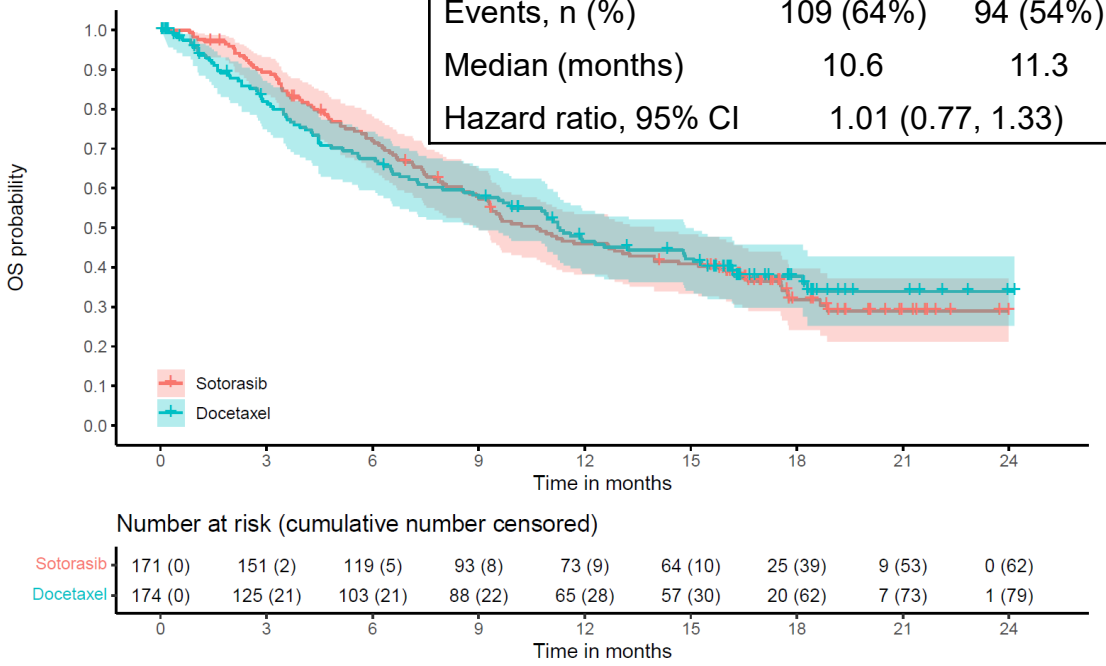
	Sotorasib	Docetaxel
Events, n (%)	122 (71%)	101 (58%)
Median (months)	5.6	4.5
Hazard ratio, 95% CI	0.66 (0.51, 0.86)	



Incremental PFS benefit (5 days – 5 weeks)
Imaging interval 6 weeks

Overall Survival

	Sotorasib	Docetaxel
Events, n (%)	109 (64%)	94 (54%)
Median (months)	10.6	11.3
Hazard ratio, 95% CI	1.01 (0.77, 1.33)	



No difference in OS (HR 1.01)

Measuring PFS Treatment Effect: Can We Quantify the Effect of Sotorasib?

Measurement	Treatment Effect Sotorasib N = 171	Robust?
Hazard ratio	Primary Analysis: 0.66 (95% CI: 0.51, 0.86) Potential overestimate if censored patients had better prognosis FDA Tipping Point Analysis: HR may lose significance	?
Median benefit	Interval censoring: 5 days to 5 weeks	X
Event rate	122 (71%) on sotorasib vs 101 (58%) on docetaxel	?
Kaplan-Meier curves	Modest initial separation that waned until about 7 months Greater separation after 7 months, but only limited patients in follow-up Overlapping pointwise confidence bands	?

Potential Bias May Impact Observed Trial Results

Signals of Systemic Bias

- Asymmetric early dropout
- Investigator imaging assessments favoring sotorasib
- Crossover before PD per BICR

Potential Impact on Estimating Treatment Effect

- Incomplete information to measure primary endpoint
- PFS per BICR confounded by investigator patient management
- Overestimation of PFS per BICR if patients who dropped out/ censored had a better prognosis

There could be many other unknown and unmeasurable effects of potential bias, including on patient selection, adverse event reporting, and patient-reported outcomes.

Applicant Acknowledges Inherent Bias

- The Applicant implemented strategies to minimize inherent bias
- However, mitigation strategies could have been improved
  - Likely not sufficient to overcome potential systemic bias
- FDA analysis shows there may not be a statistically significant treatment benefit for sotorasib over docetaxel
  - If there is, it is not reliably quantifiable

CodeBreaK 200 Study Design vs Study Conduct

Study Design Features:

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

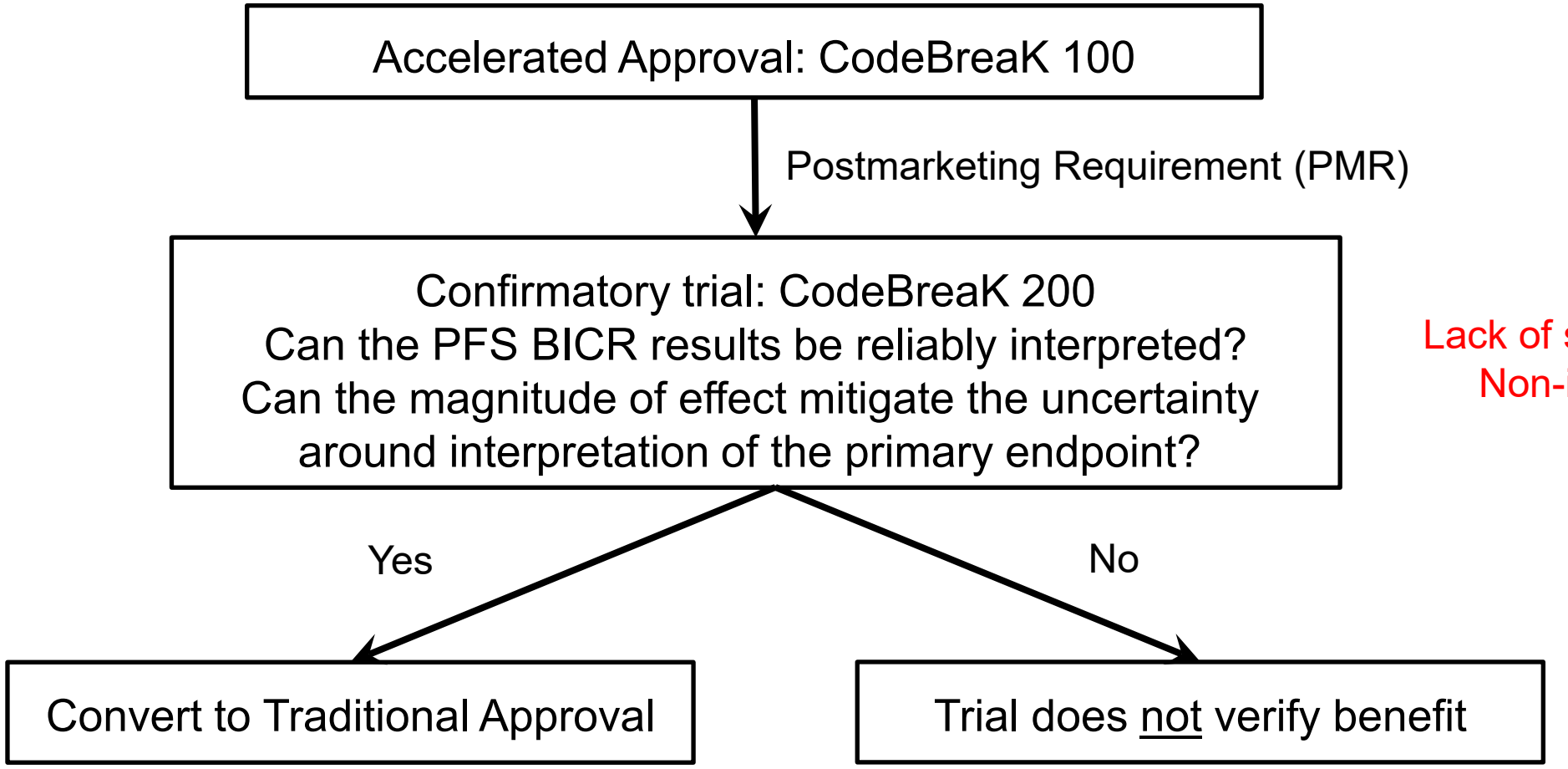
Study Conduct Issues:

- Lack of adherence to protocol and imaging charter (potential misuse of COP)
- 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

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

Regulatory Considerations



Lack of superiority ≠ Non-inferiority

Regulatory Considerations

- After a confirmatory trial fails to verify benefit, the regulatory decision to withdraw an accelerated approval is not automatic

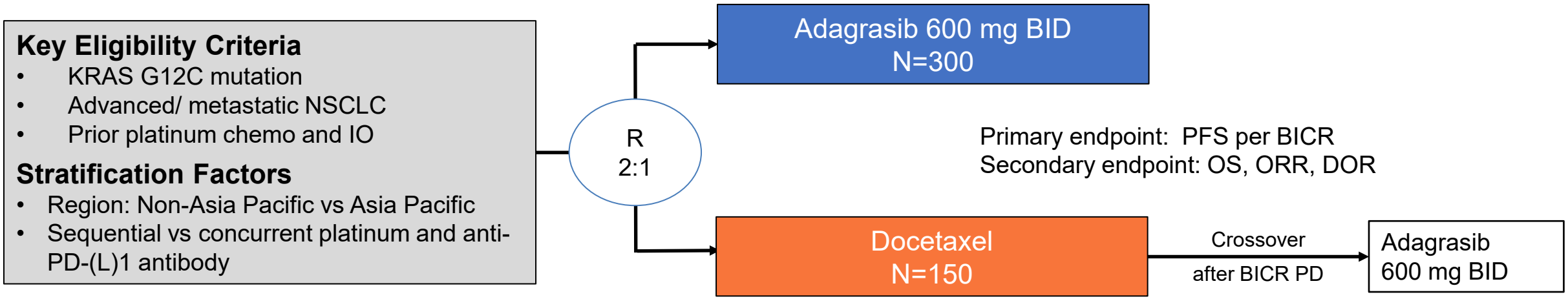
- Decision is affected by:
  - Overall results of the confirmatory trial (e.g., survival detriment?)
  - Current benefit-risk assessment, rather than at the time of the accelerated approval
  - Potential safety advantage of the drug

Adagrasib Accelerated Approval

KRYSTAL-1	Adagrasib 600 mg BID N = 112
Objective response rate per BICR, % (95% CI)	43 (34, 53)
Median duration of response, mos (95% CI)	8.5 (6.2, 13.8)

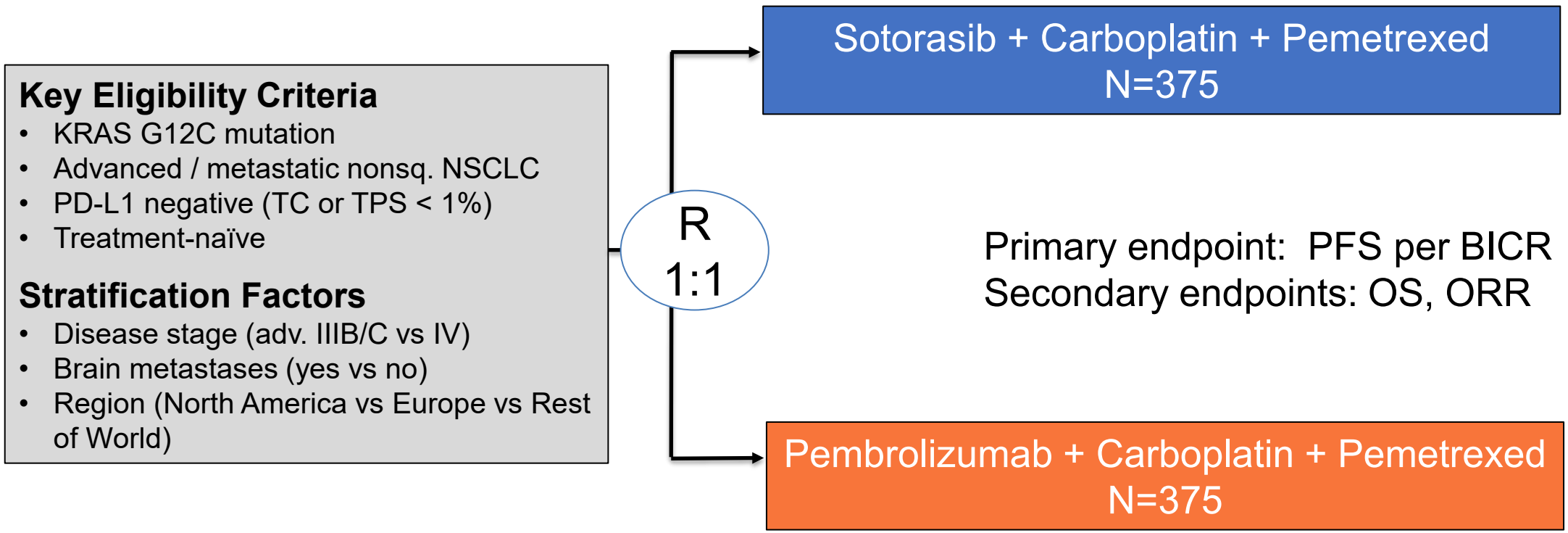
Source: KRIZATI (adagrasib) USPI

Confirmatory Trial: KRYSTAL-12



PD-(L)1: programmed cell death-1/programmed death ligand-1

First Line Trial of Sotorasib: CodeBreaK 202



Adv. = advanced; Nonsq: non-squamous; TC: tumor cells; TPS: tumor proportion score

Discussion Points

Given multiple regulatory pathways and the evolving therapeutic landscape, FDA is not seeking the advice of the Committee as to whether CodeBreaK 200 should be used to convert the accelerated approval to traditional approval for sotorasib.

Rather, we are asking the Committee to discuss the findings of CodeBreaK 200, the multiple signals of potential bias, and if the PFS per BICR treatment effect can be reliably interpreted.

Voting Question

Can the primary endpoint, PFS per BICR, be reliably interpreted in CodeBreaK 200?

Thank You

FDA recognizes the time and effort necessary to conduct cancer clinical trials. We would like to particularly thank the patients and their families as well as the investigators and research staff who participated in the research studies discussed today.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ADMINISTRATION

OS Comparison Among the Patients who Started New Anticancer Therapy before BICR PD

From Randomization	Sotorasib N = 24	Docetaxel N = 31
Median OS, months (95% CI)	11.2	18.6
OS events, n (%)	16 (67)	18 (58)
HR (95% CI)	1.44 (0.73, 2.83)	

Post Censoring for new anticancer therapy	Sotorasib N = 24	Docetaxel N = 31
Median OS, months (95% CI)	7.1	13.7
OS events, n (%)	16 (67)	18 (58)
HR (95% CI)	1.80 (0.92, 3.55)	

Favorable overall survival for the patients in docetaxel arm

OS Comparison Among the Patients who Started New Anticancer Therapy before BICR PD

From Randomization	Sotorasib (n=24)	Docetaxel (n=31)	
		Crossover (n=19)	Other (n=12)
Median OS, months (95% CI)	11.2	24.4	11.2
OS events, n (%)	16 (67)	9 (47)	9 (75)
HR (95% CI)	1.44 (0.73, 2.83)		

Post Censoring for New Anti Cancer Therapy	Sotorasib (n=24)	Docetaxel (n=31)	
		Crossover (n=19)	Other (n=12)
Median OS, months (95% CI)	7.1	17.7	9.2
OS events, n (%)	16 (67)	9 (47)	9 (75)
HR (95% CI)	1.80 (0.92, 3.55)		

Favorable overall survival for the patients in docetaxel arm

Sensitivity Analyses: New Anticancer Therapy before BICR PD

Analysis	Sotorasib mPFS	Docetaxel mPFS	HR (95% CI)
All new anticancer therapy as an event	4.4 months	3.7 months	0.66 (0.51, 0.86)
New anticancer therapy in sotorasib arm only as an event	4.4 months	4.5 months	0.77 (0.59, **1.01**)
New anticancer therapy as an events except for early crossover patients	4.4 months	4.0 months	0.72 (0.56, **0.94**)
Use BICR call of PD regardless of new anticancer therapy*	5.6 months	4.5 months	0.73 (0.56, **0.95**)

*Treatment policy analysis