Sotorasib for the Treatment of Adult Patients with *KRAS p.G12C*-mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Oncologic Drugs Advisory Committee

October 5, 2023

Introduction

Jackie Kline, PhD

Vice President, Global Regulatory Affairs
Amgen Inc.

Confirmatory Study CodeBreaK 200
Demonstrates Clinical Benefit of Sotorasib

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

KRAS p.G12C=KRAS gene with a mutation resulting in a G12C amino acid substitution at the protein level;
NSCLC = Non-Small Cell Lung Cancer

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CONFIRMATORY STUDY

CodeBreaK 200
PHASE 3

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

Sotorasib vs Docetaxel
N=345

KRAS p.G12C=KRAS gene with a mutation resulting in a G12C amino acid substitution at the protein level;
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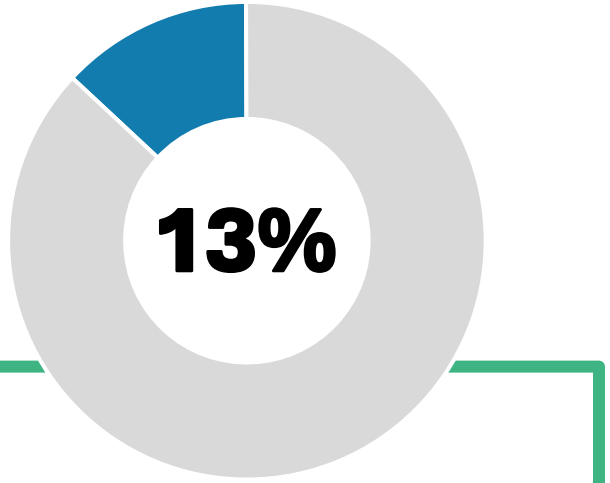
Sotorasib Selectively Inhibits KRAS^{G12C} Mutant Protein

***KRAS p.G12C* Mutation**



1 in 8 patients (13%) with lung adenocarcinomas have a *KRAS p.G12C* mutation[1]

1. Nassar AF, et al. *N Engl J. Med*. 2021;384:185-187.

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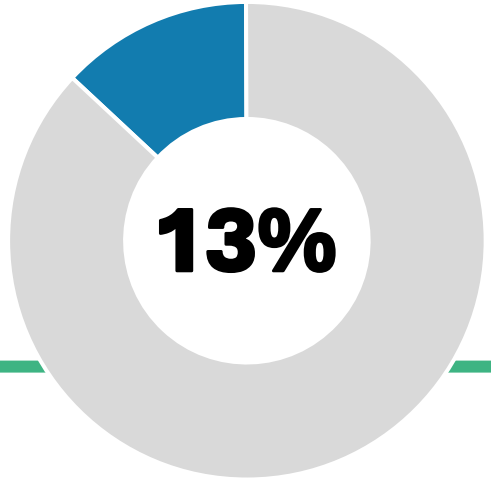

1 in 8 patients (13%) with lung adenocarcinomas have a *KRAS p.G12C* mutation[1]

- ***KRAS p.G12C* is a single point driver mutation**
- **Sotorasib covalently binds to mutated KRAS^{G12C} protein**
  - Locks protein in an inactive state
  - Inhibits tumor cell growth

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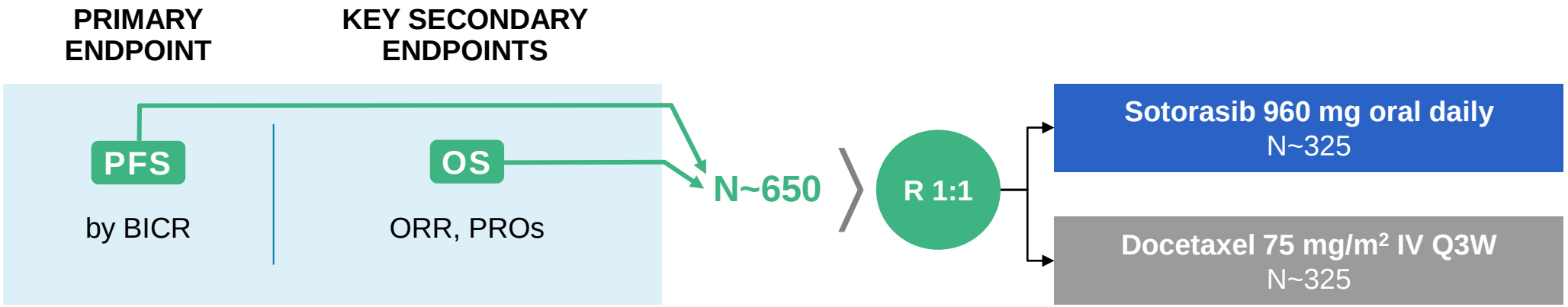
Design of CodeBreaK 200 Evolved in Response to Emerging Data from CodeBreaK 100



PFS=progression-free survival, BICR=blinded independent central review, OS=overall survival, ORR=objective response rate, PROs=patient reported outcomes

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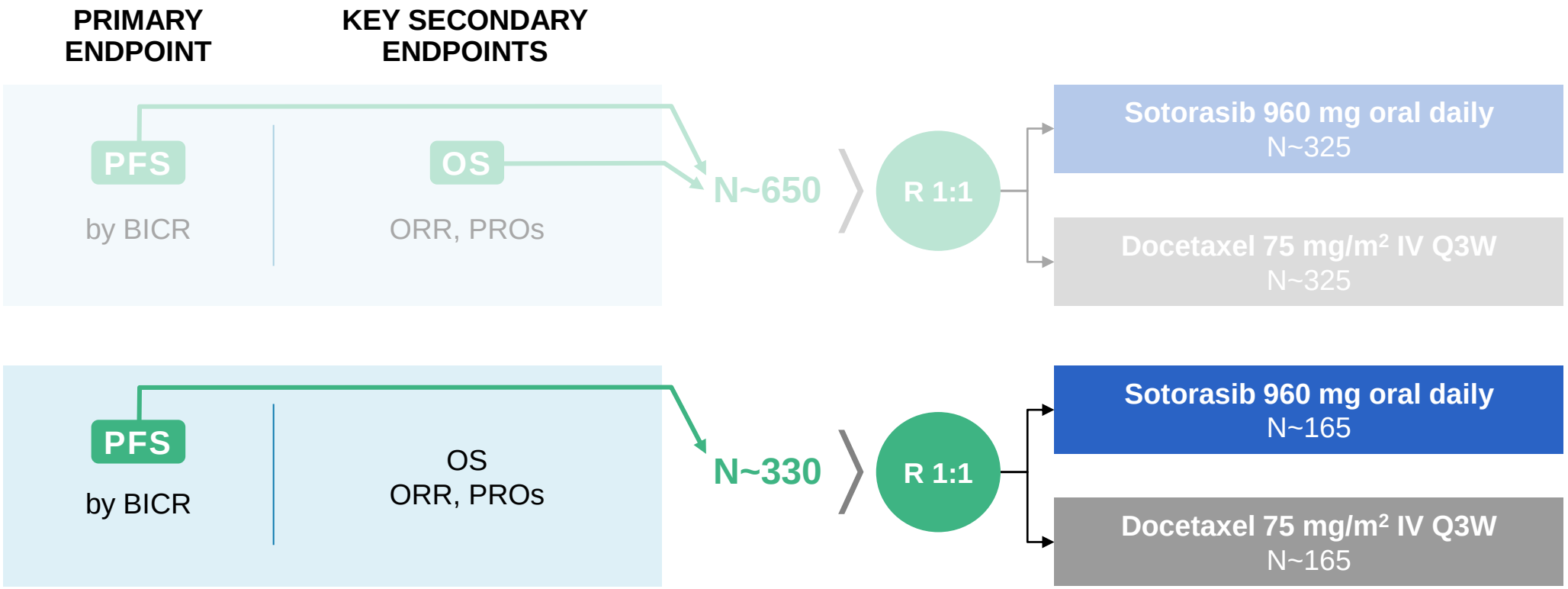

Amendment maintained adequate power for PFS but not OS

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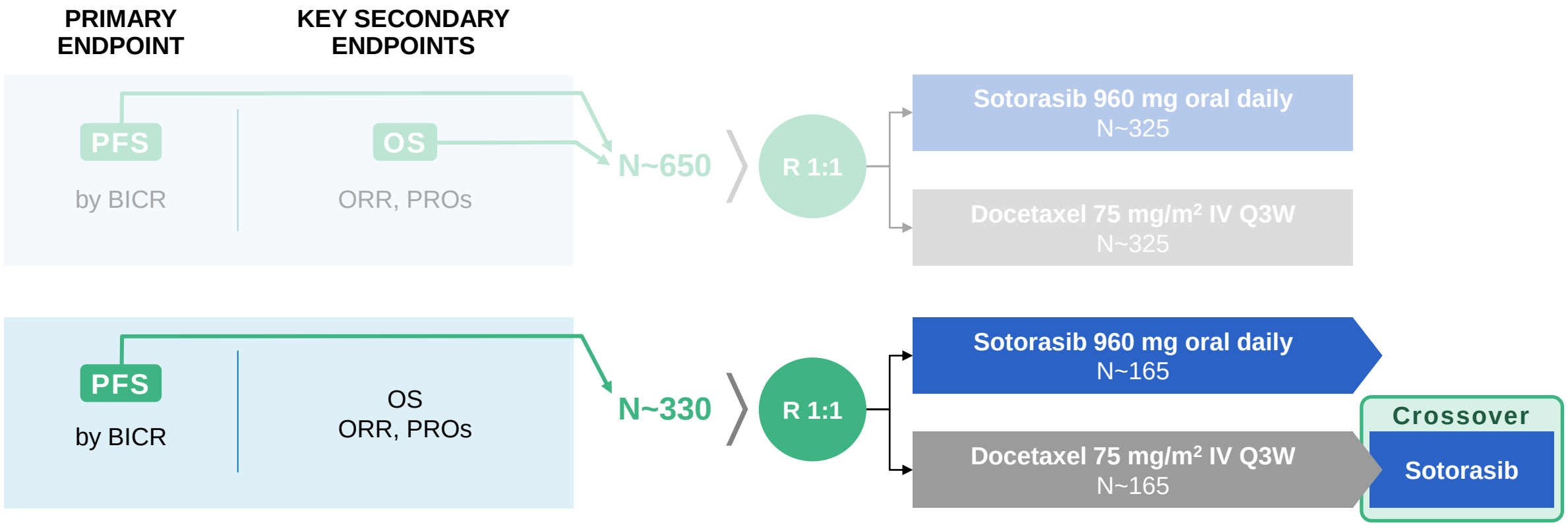

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What You Will Hear Today

Efficacy

Bhakti Mehta, MD, MPH

Sotorasib improved progression-free survival over docetaxel and resulted in rapid and durable tumor response

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Sotorasib exhibits a differentiated safety profile as compared to docetaxel

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Clinical Perspective

Melissa Johnson, MD

Sotorasib provides an important targeted treatment option for patients with NSCLC who have received prior systemic therapy

Additional Subject Matter Expert

Gary Koch, PhD
Professor, Department of Biostatistics; Director, Biometric Consulting Laboratory
University of North Carolina at Chapel Hill

Efficacy

Bhakti Mehta, MD, MPH

Executive Medical Director, Global Clinical Development
Amgen Inc.

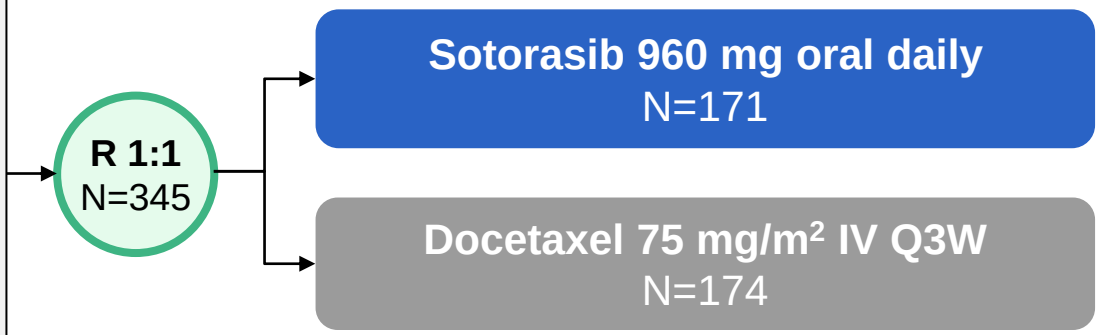
CodeBreaK 200 Phase 3 Study Design

Key Eligibility Criteria

- *KRAS p.G12C* mutation
- Advanced NSCLC
- **≥1 prior treatment including platinum-based chemotherapy and checkpoint inhibitor**
- No active brain metastases
- ECOG ≤1

Stratification Factors

- Prior lines of therapy (1 vs 2 vs >2)
- Race (Asian vs non-Asian)
- History of CNS involvement (yes vs no)

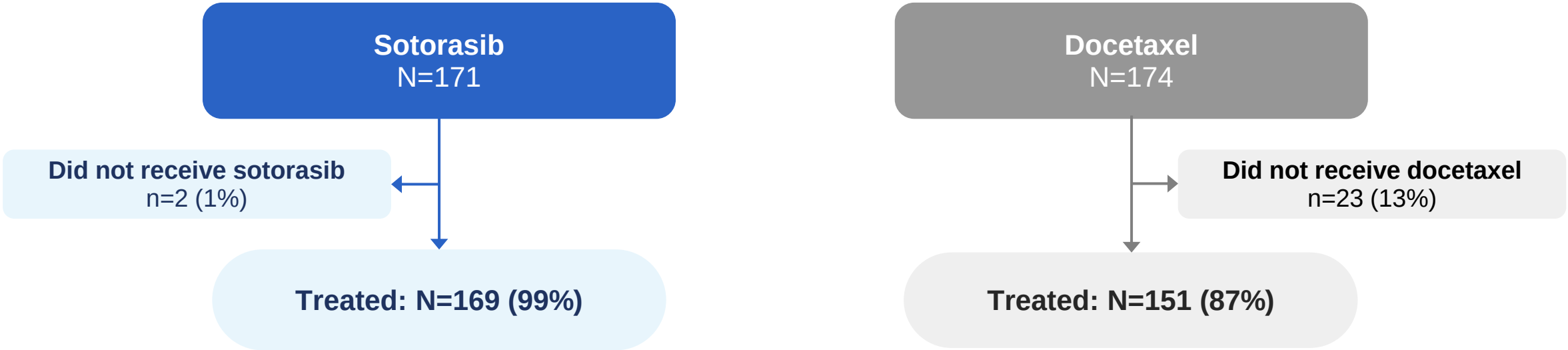


Primary Endpoint: PFS by Blinded Independent Central Review

Secondary Endpoints: Efficacy (OS, ORR, DOR, TTR, DCR), PROs, safety/tolerability

ECOG=Eastern Cooperative Oncology Group; CNS=central nervous system; DOR=duration of response; TTR=time to response; DCR=disease control rate

Patient Disposition



Data cutoff: 02 August 2022 (Primary Analysis), 148 centers in 22 countries

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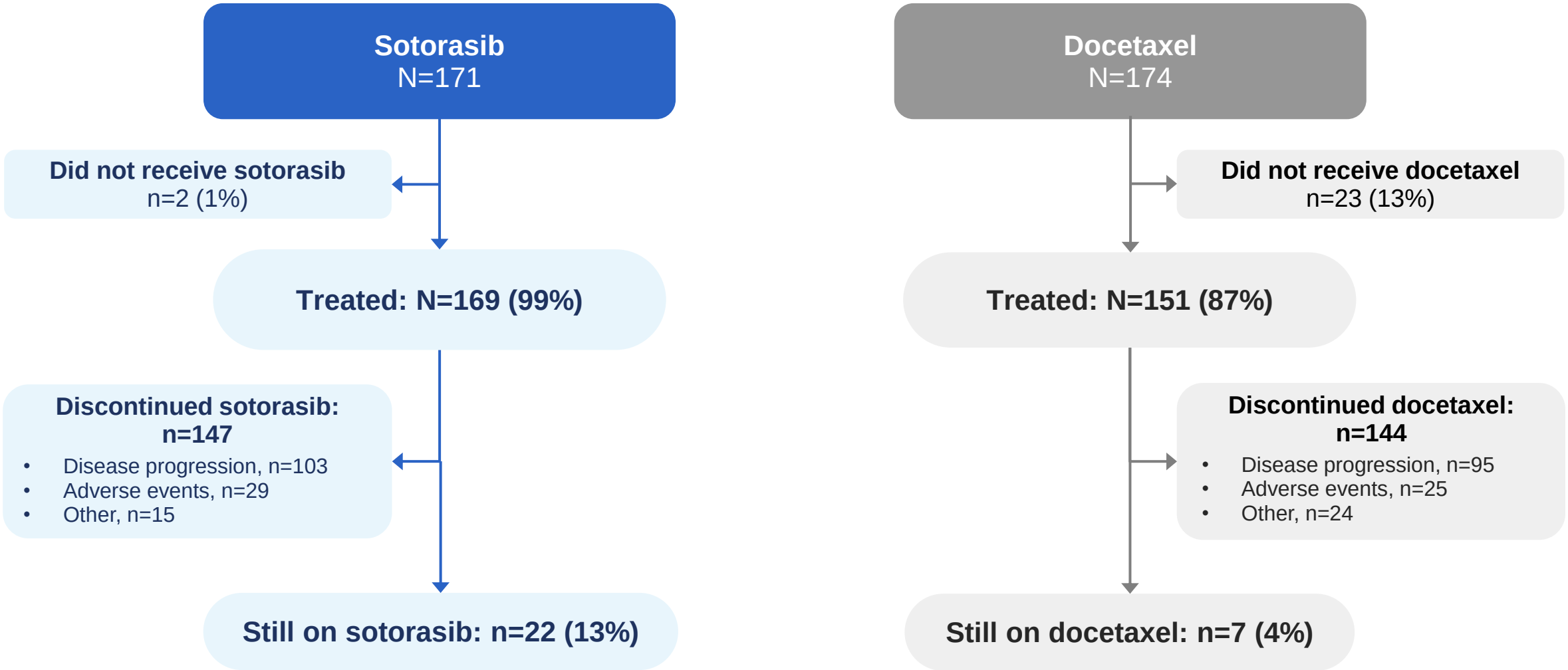

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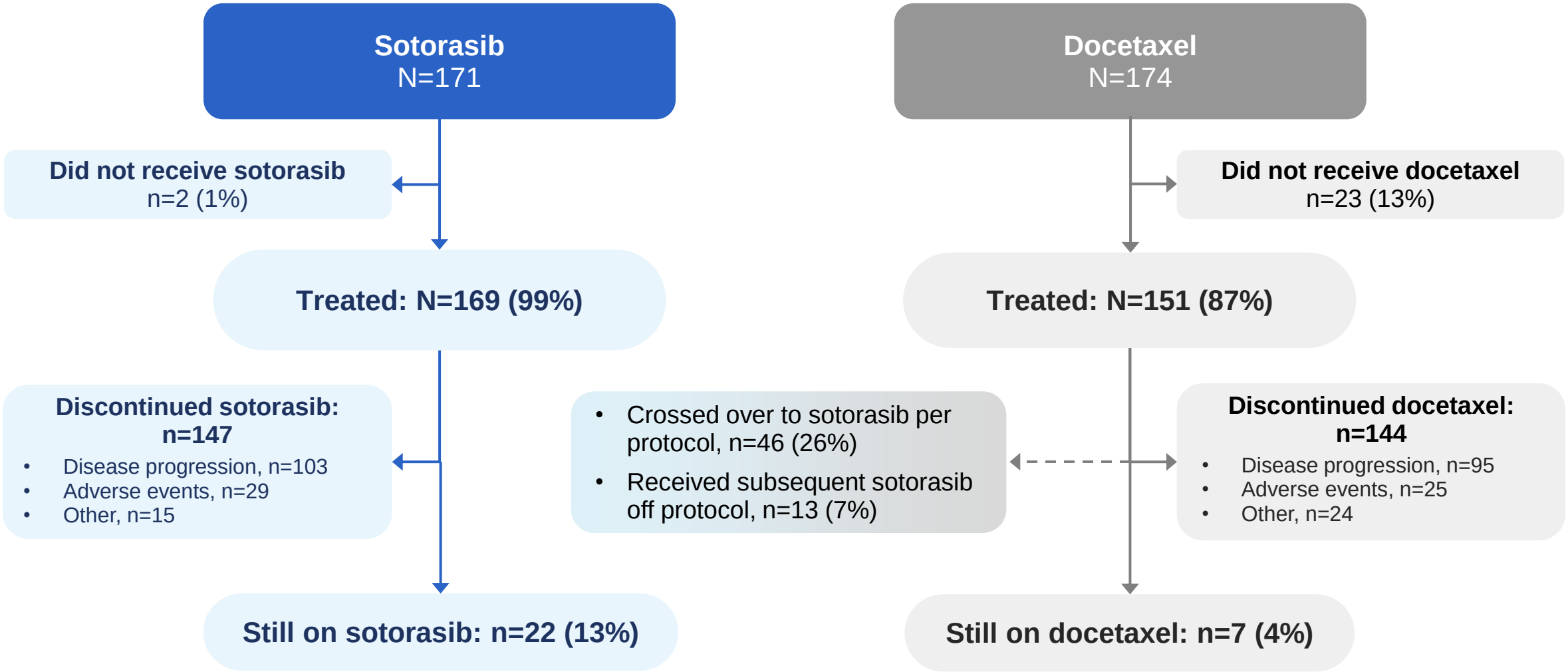

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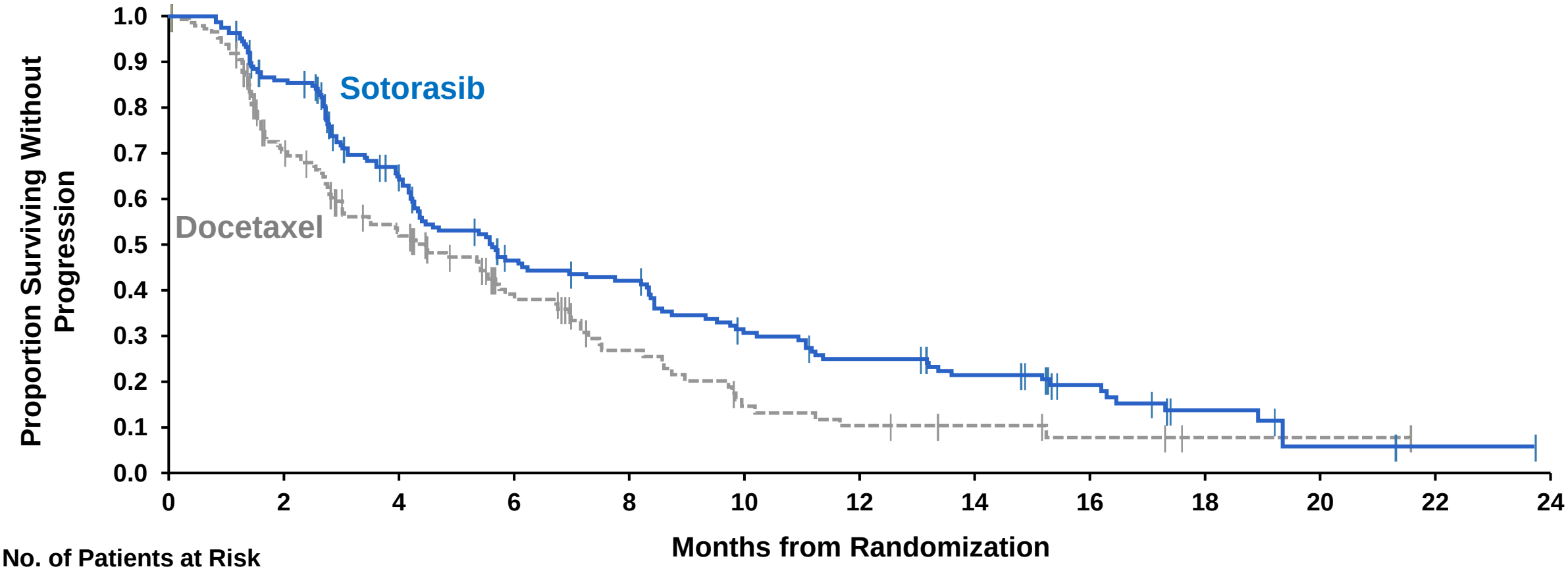
Baseline Characteristics: Well Balanced

	Sotorasib 960 mg Oral Daily N=171	Docetaxel 75 mg/m^2 IV Q3W N=174
Age, years, median (range)	64 (32, 88)	64 (35, 87)
North America/Europe/Other, %	12 / 74 / 15	13 / 72 / 15
Smoking history (current or former), n (%)	166 (97)	166 (95)
ECOG performance status 1, n (%)	112 (65)	115 (66)
History of CNS involvement, n (%)	58 (34)	60 (34)
Liver metastasis, n (%)	30 (18)	35 (20)
Prior lines of therapy, n (%)		
1	77 (45)	78 (45)
2	65 (38)	69 (40)
>2	29 (17)	27 (16)

Primary Endpoint Met – PFS by BICR

Sotorasib Reduces Risk of Progression or Death by 34%



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	

Median study follow-up: 17.7 months

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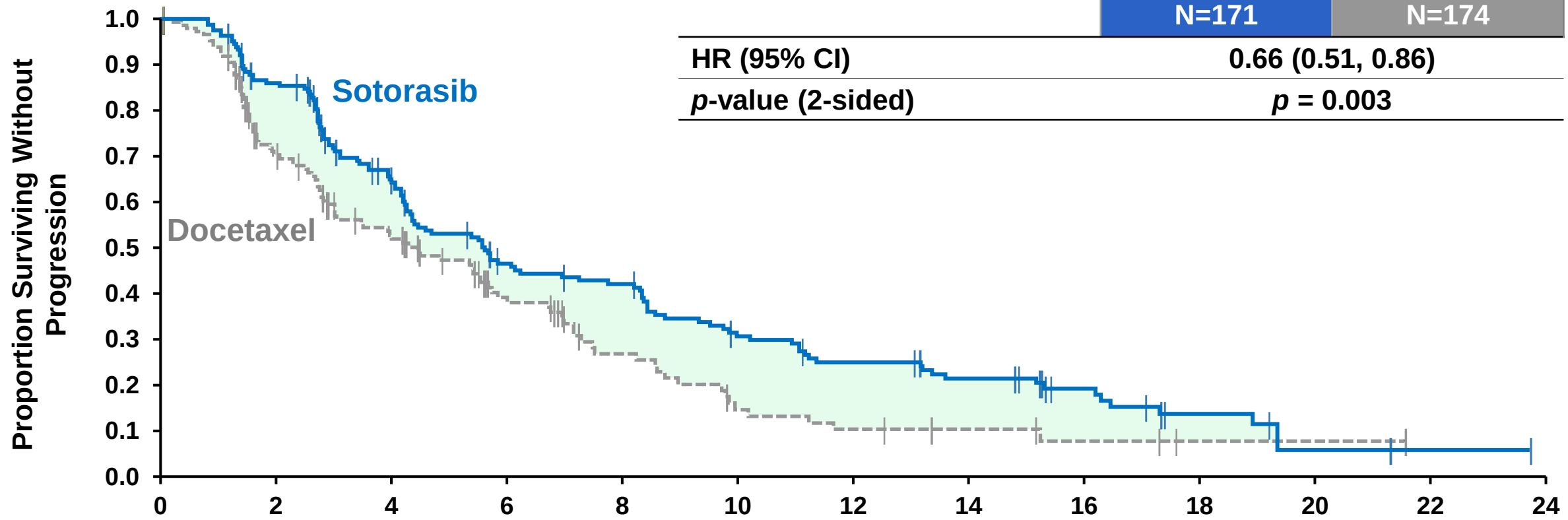
Sotorasib Reduces Risk of Progression or Death by 34%

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



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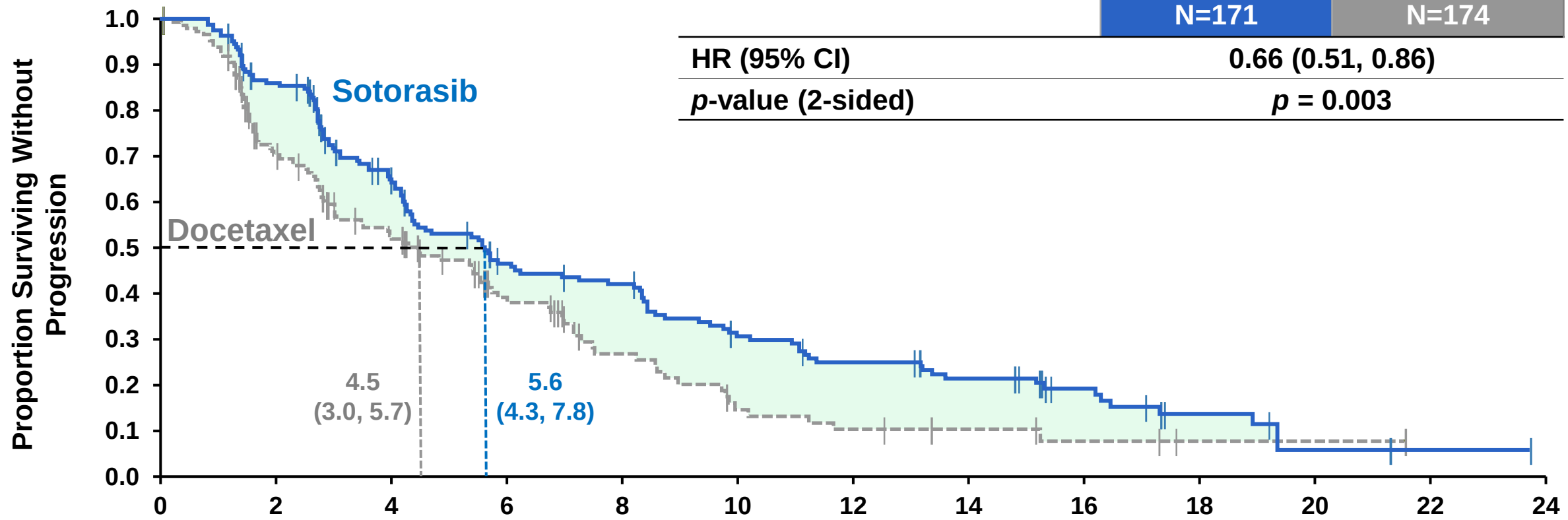

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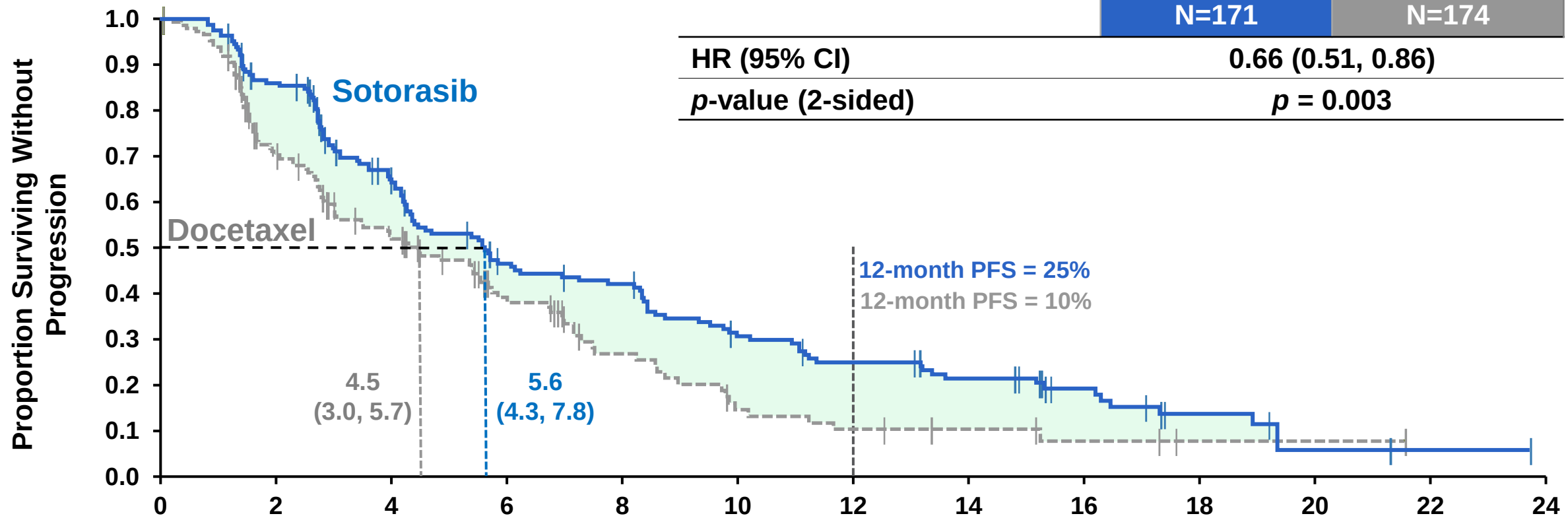

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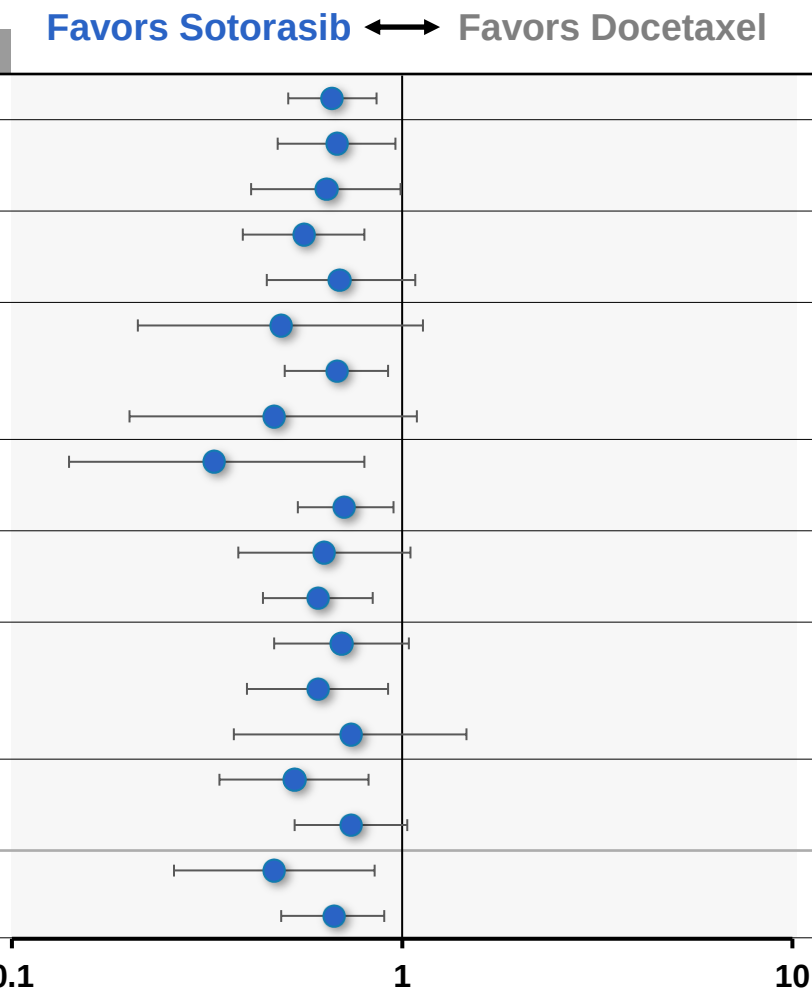
PFS Primary Analyses

PFS Results Favor Sotorasib Across All Key Subgroups

Subgroup		Patients, n Sotorasib	Patients, n Docetaxel	HR (95%CI)
All randomized patients		171	174	**0.66** (0.51, 0.86)
Age at baseline, yrs	**<65**	91	95	**0.68** (0.48, 0.96)
	≥65	80	79	**0.64** (0.41, 0.99)
Sex	**Male**	109	95	**0.56** (0.39, 0.80)
	Female	62	79	**0.69** (0.45, 1.08)
Region	**North America**	20	22	**0.49** (0.21, 1.13)
	Europe	126	126	**0.68** (0.50, 0.92)
	Other	25	26	**0.47** (0.20, 1.09)
Race	**Asian**	21	22	**0.33** (0.14, 0.80)
	Non-Asian	149	151	**0.71** (0.54, 0.95)
Baseline ECOG status	**0**	59	59	**0.63** (0.38, 1.05)
	1	112	115	**0.61** (0.44, 0.84)
Number of prior lines in advanced disease	**1**	77	78	**0.70** (0.47, 1.04)
	2	65	69	**0.61** (0.40, 0.92)
	>2	29	27	**0.74** (0.37, 1.46)
History of CNS involvement	**Yes**	58	60	**0.53** (0.34, 0.82)
	No	113	114	**0.74** (0.53, 1.03)
Liver metastasis	**Yes**	30	35	**0.47** (0.26, 0.85)
	No	141	139	**0.67** (0.49, 0.90)



Pre-Specified PFS Sensitivity Analysis Showed Consistent Treatment Effect

Anticipated Bias	Pre-Specified Sensitivity Analysis	PFS Results HR (95% CI)
Investigator assessment	PFS per investigator assessment	**0.65** (0.50, 0.82)

Data cut-off date=02AUG2022;

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BICR PFS censored due to new anti-cancer therapy	Treating new anti-cancer therapy as a PFS event	**0.60** (0.47, 0.76)

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BICR PFS censored due to new anti-cancer therapy	Treating new anti-cancer therapy as a PFS event	**0.60** (0.47, 0.76)
BICR PFS censored due to withdrawal of consent or loss to follow-up (LTFU)	Treating LTFU/Withdrawal of consent as a PFS event	**0.65** (0.50, 0.85)

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BICR PFS censored due to withdrawal of consent or loss to follow-up (LTFU)	Treating LTFU/Withdrawal of consent as a PFS event	**0.65** (0.50, 0.85)
Actual assessment date is different than scheduled assessment date	Analysis based on scheduled assessment dates instead of actual assessment dates	**0.66** (0.51, 0.86)

Data cut-off date=02AUG2022;

Sotorasib Achieved Significantly Higher Objective Response Rate vs. Docetaxel (p<0.001)

% (95% CI)	Sotorasib	Docetaxel
ORR	28 (22, 35)	13 (9, 19)

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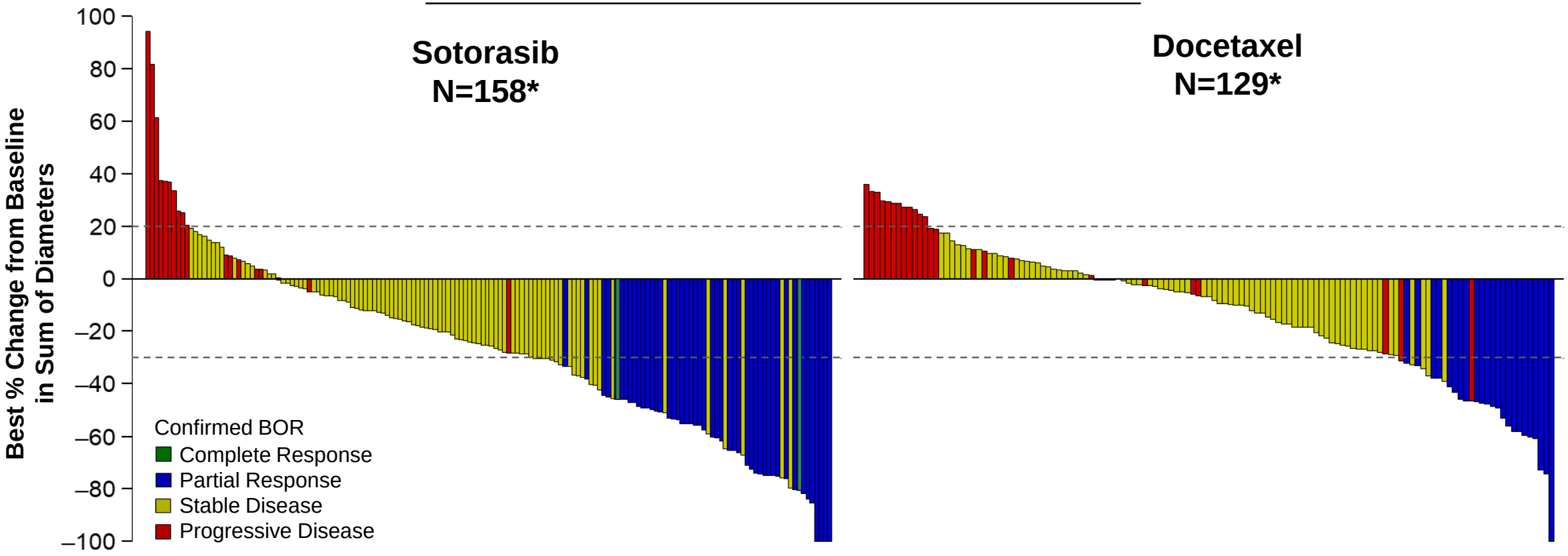
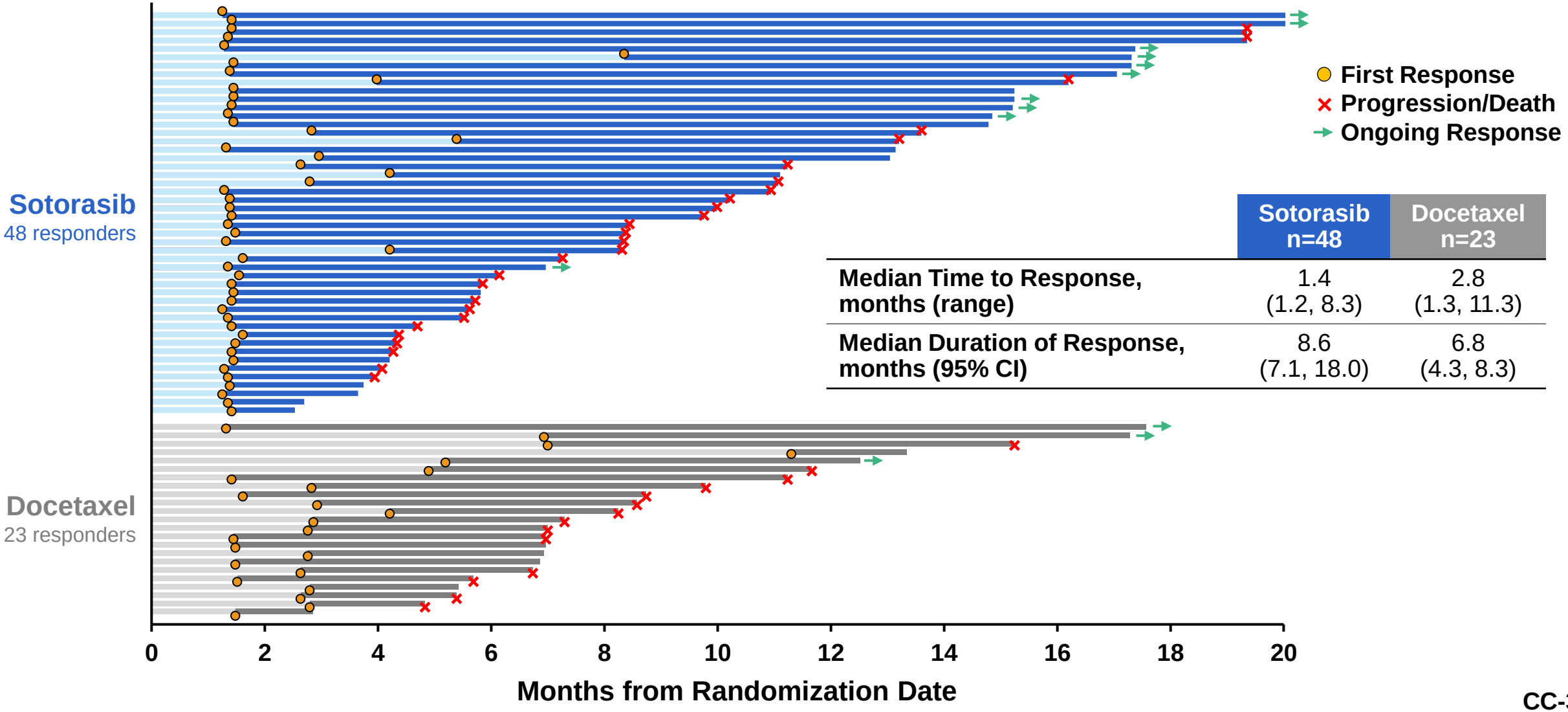
% (95% CI)	Sotorasib	Docetaxel
ORR	**28 (22, 35)**	**13 (9, 19)**
DCR	**83** (76, 88)	**60** (53, 68)



*Patients without baseline target lesions or post-baseline percent changes, or with BOR of NE are not shown.

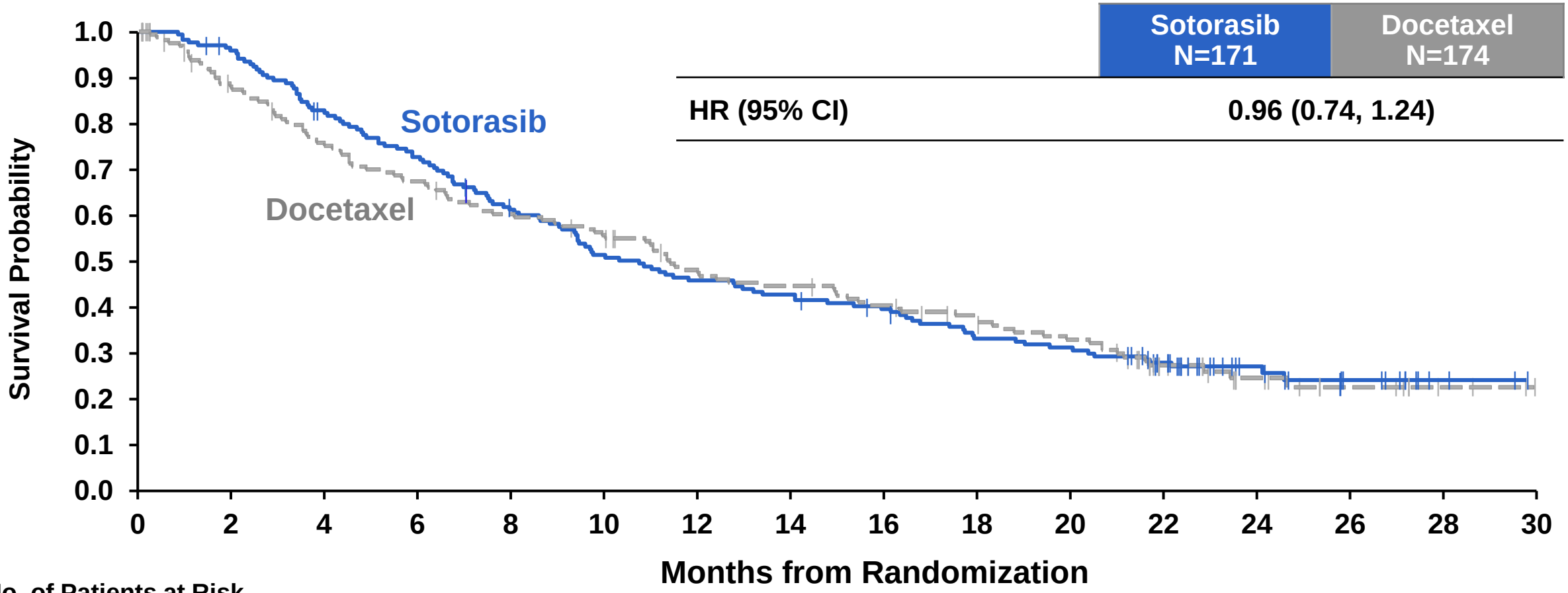
Sotorasib Induced Faster and Longer Lasting Responses in More Patients Than Docetaxel



	Sotorasib n=48	Docetaxel n=23
Median Time to Response, months (range)	1.4 (1.2, 8.3)	2.8 (1.3, 11.3)
Median Duration of Response, months (95% CI)	8.6 (7.1, 18.0)	6.8 (4.3, 8.3)

Sotorasib and Docetaxel Overall Survival Overlap

Data Cut-off: 18-JAN-2023

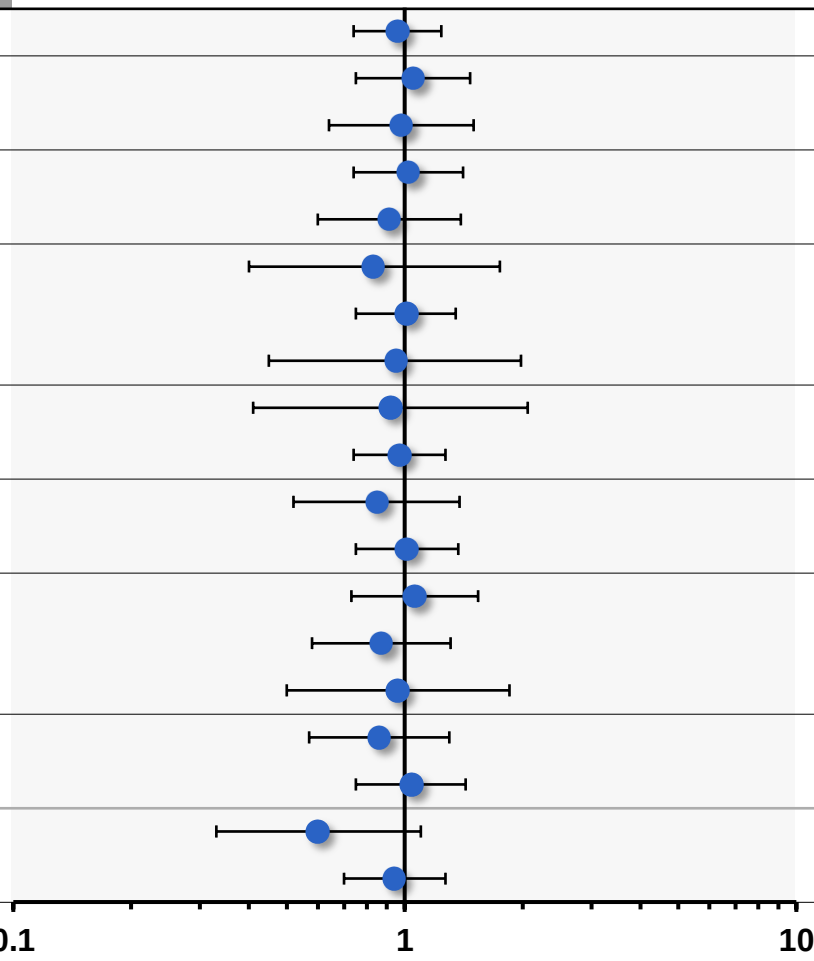


No. of Patients at Risk

Sotorasib	171	162	137	120	98	82	74	67	62	51	47	32	17	11	2	0
Docetaxel	174	136	116	104	91	82	67	64	57	48	43	23	13	8	3	0

Overall Survival by Subgroup

Subgroup		Patients, n Sotorasib	Patients, n Docetaxel	OS HR (95%CI)
All randomized patients		171	174	**0.96** (0.74, 1.24)
Age at baseline, yrs	<65	91	95	**1.05** (0.75, 1.47)
	≥65	80	79	**0.98** (0.64, 1.50)
Sex	Male	109	95	**1.02** (0.74, 1.41)
	Female	62	79	**0.91** (0.60, 1.39)
Region	North America	20	22	**0.83** (0.40, 1.75)
	Europe	126	126	**1.01** (0.75, 1.35)
	Other*	25	26	**0.95** (0.45, 1.98)
Race	Asian	21	22	**0.92** (0.41, 2.06)
	Non-Asian	149	151	**0.97** (0.74, 1.27)
Baseline ECOG status	0	59	59	**0.85** (0.52, 1.38)
	1	112	115	**1.01** (0.75, 1.37)
Number of prior lines in advanced disease	1	77	78	**1.06** (0.73, 1.54)
	2	65	69	**0.87** (0.58, 1.31)
	>2	29	27	**0.96** (0.50, 1.85)
History of CNS involvement	Yes	58	60	**0.86** (0.57, 1.30)
	No	113	114	**1.04** (0.75, 1.43)
Liver metastasis	Yes	30	35	**0.60** (0.33, 1.10)
	No	141	139	**0.94** (0.70, 1.27)



Data cutoff: 18 Jan 2023
*Other includes South America, Asia, and Australia

PRO Measures and Analyses in CodeBreaK 200
Overview

PRO Measures
EORTC QLQ-C30
EORTC QLQ-LC13
EQ-5D-5L/VAS
GP5 of FACT-G
PGIS
PGIC
PRO-CTCAE
BPI-SF

PROs not formally statistically tested due to hierarchical testing rules

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Analysis Endpoints

- **Change from baseline to Week 12**
- **Time to deterioration**
- **Descriptive statistics** (mean scores / % of patients over time, CDF)

CDF=cumulative distribution function
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→ Time to Deterioration in GHS/QoL, physical functioning, chest pain, cough, dyspnea

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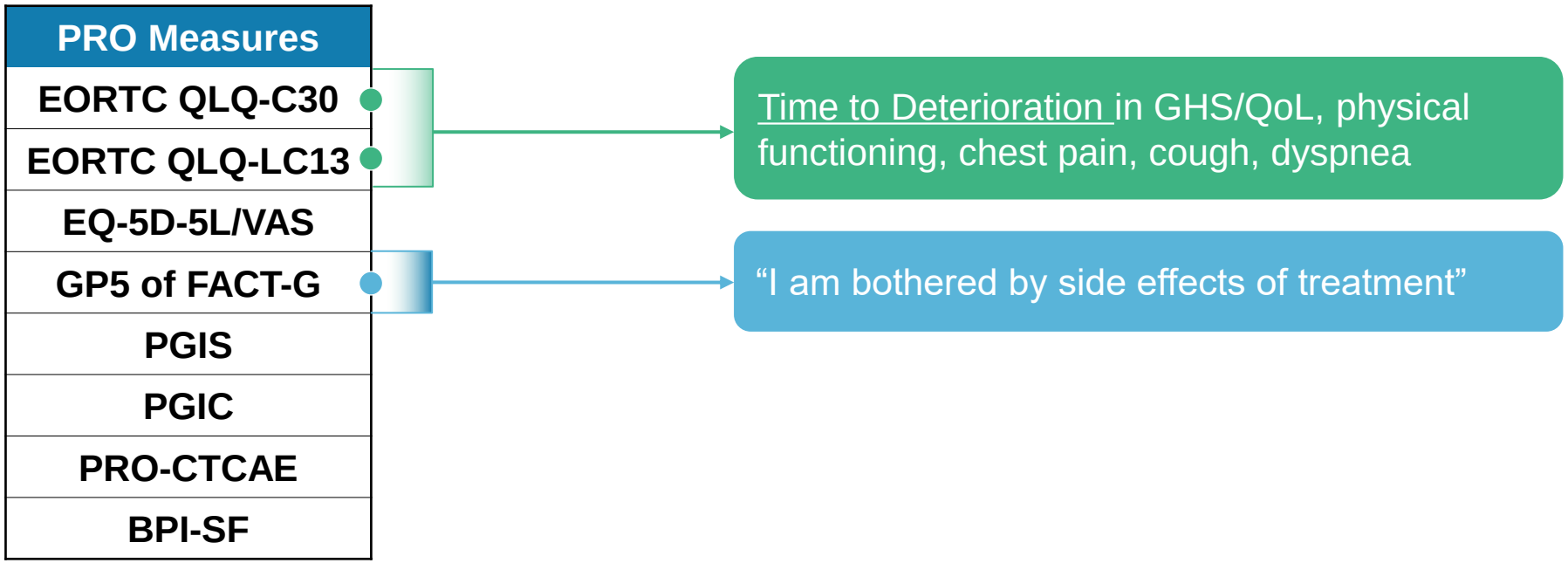

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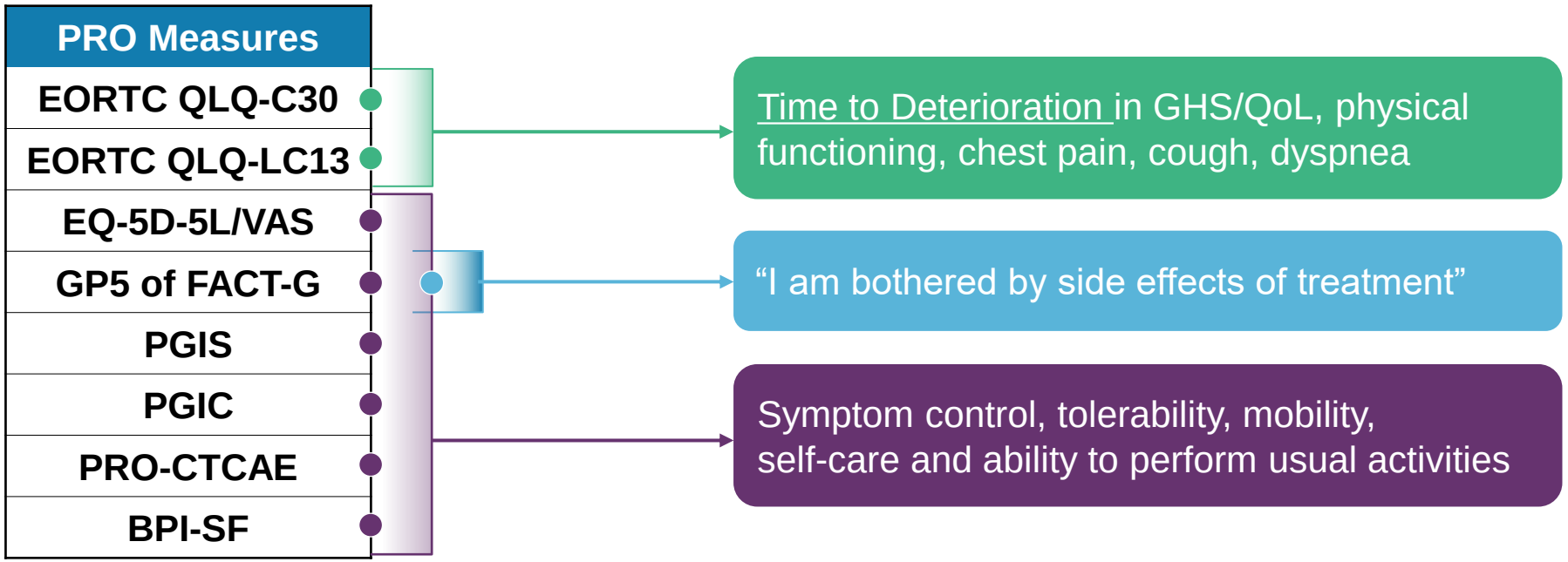

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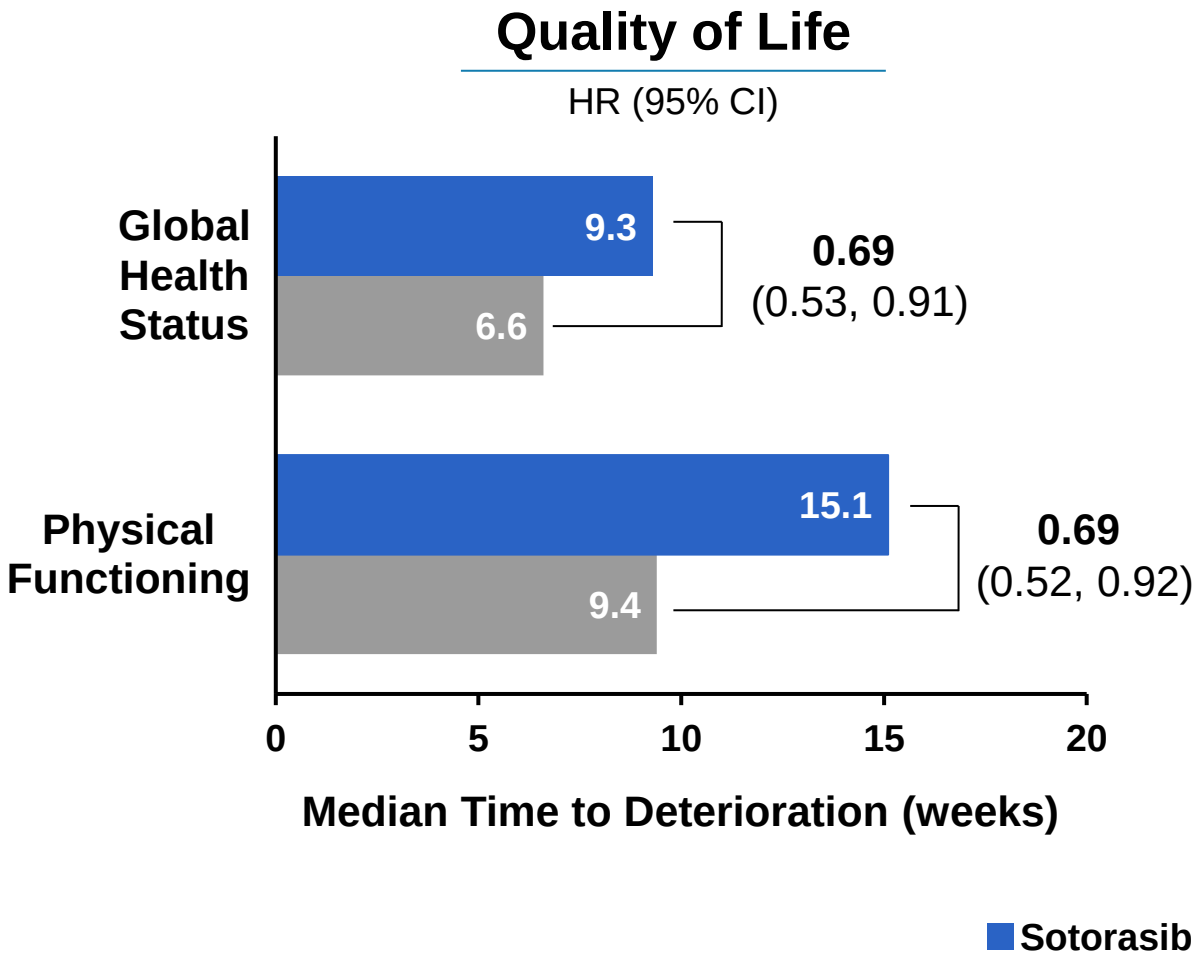
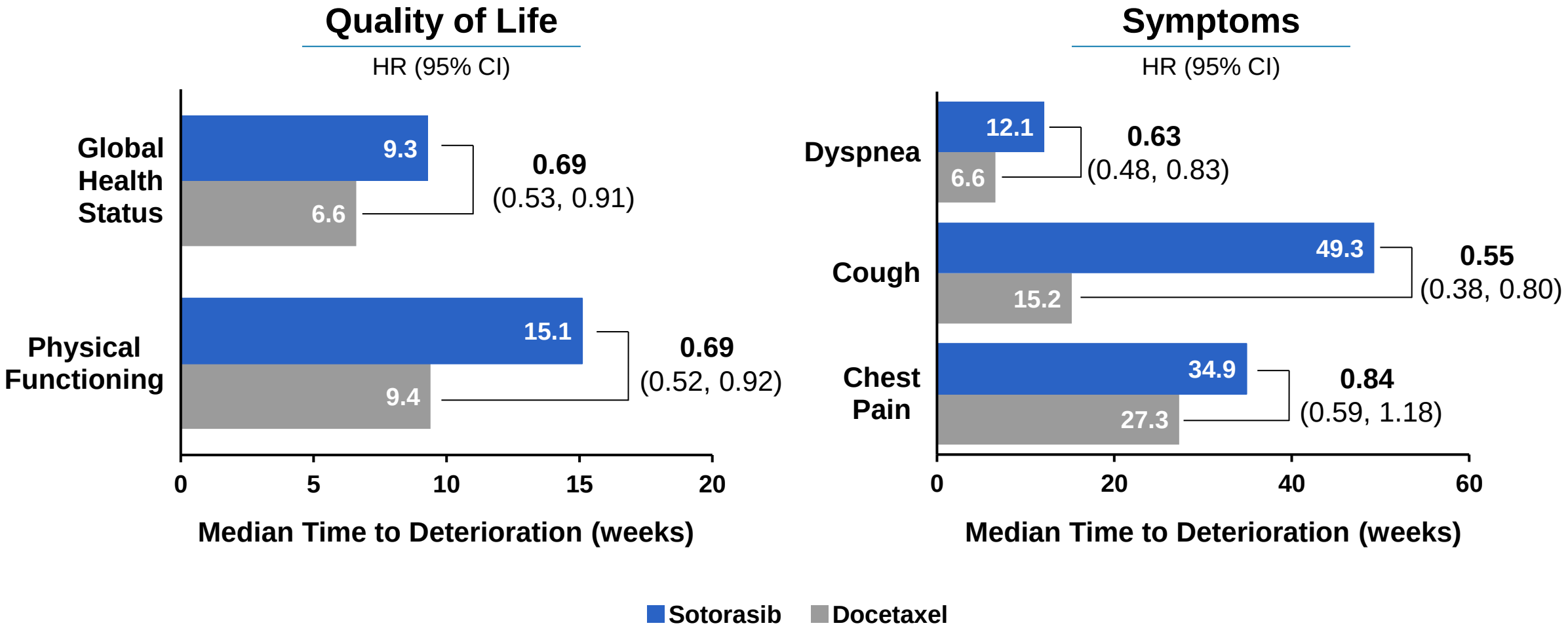
PRO: Sotorasib Improved Time to Deterioration



PRO: Sotorasib Improved Time to Deterioration



CodeBreaK 200 Confirms Clinical Benefit of Sotorasib

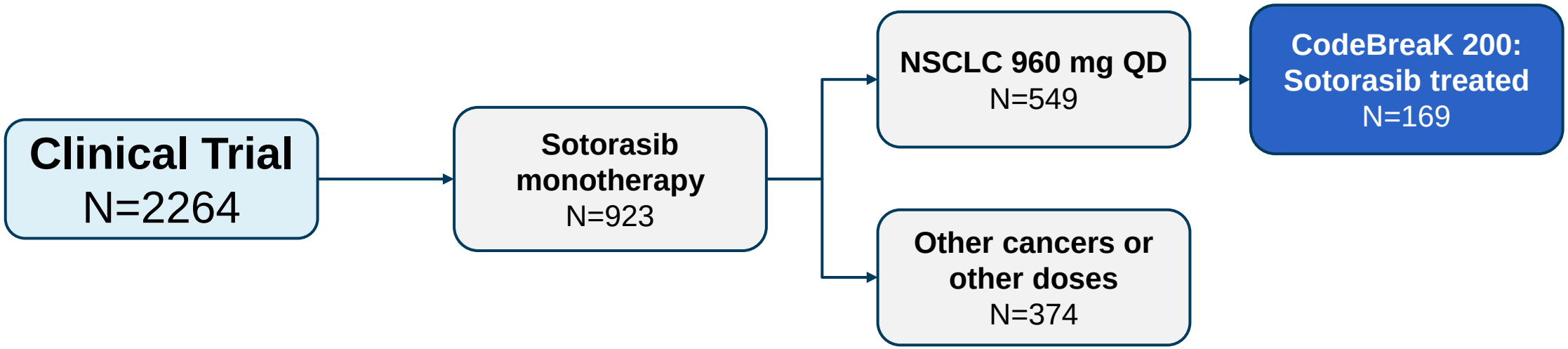
- **Sotorasib improved PFS vs. docetaxel**
- **PFS benefit was consistent and statistically robust**
  - Between central and investigator review
  - Across subgroups
  - In prespecified sensitivity analyses
- **Sotorasib improved ORR, DCR, TTR, and DOR vs. docetaxel**
- **OS was similar**
- **Patient reported outcomes favored sotorasib**

Safety

Osa Eisele, MD, MPH

Executive Medical Director, Global Patient Safety
Amgen Inc.

Safety Profile Supported by a Robust Safety Database

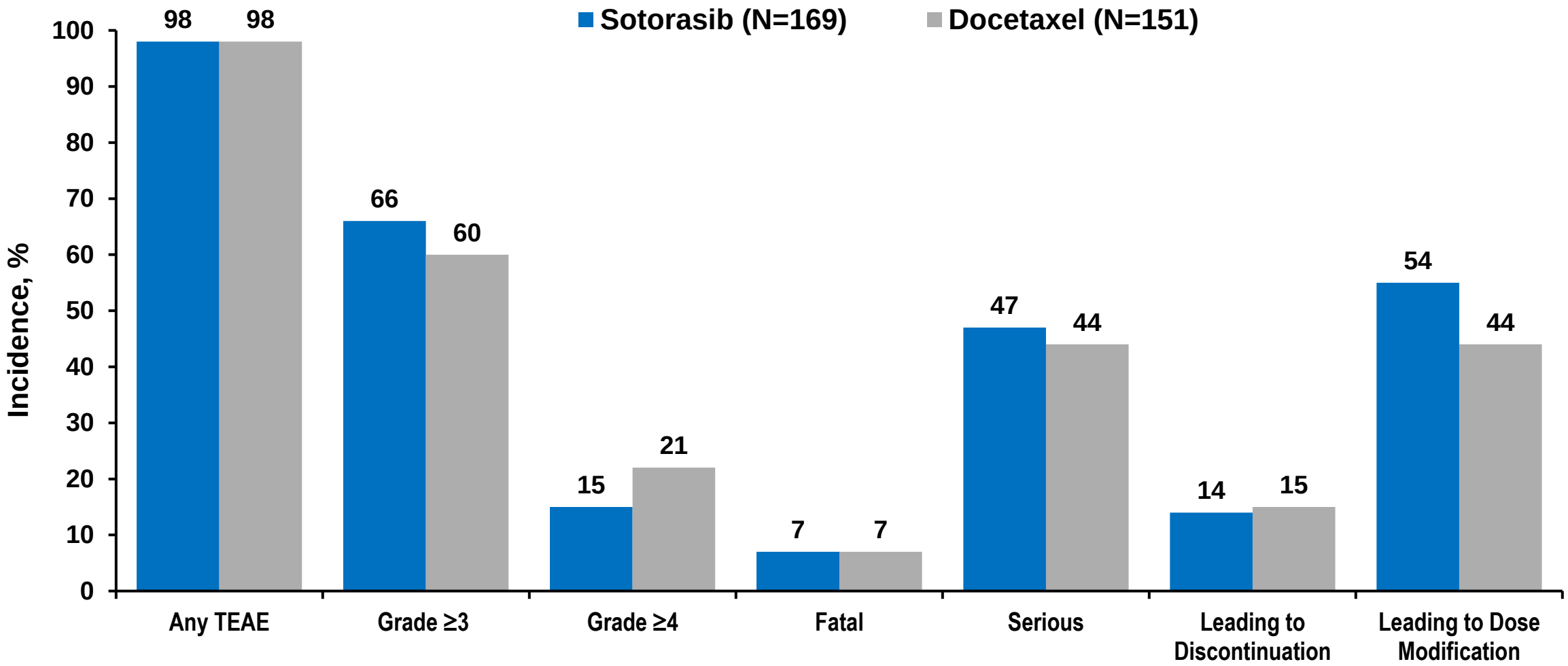


Established safety profile supported by an extensive clinical trial program and postmarketing experience

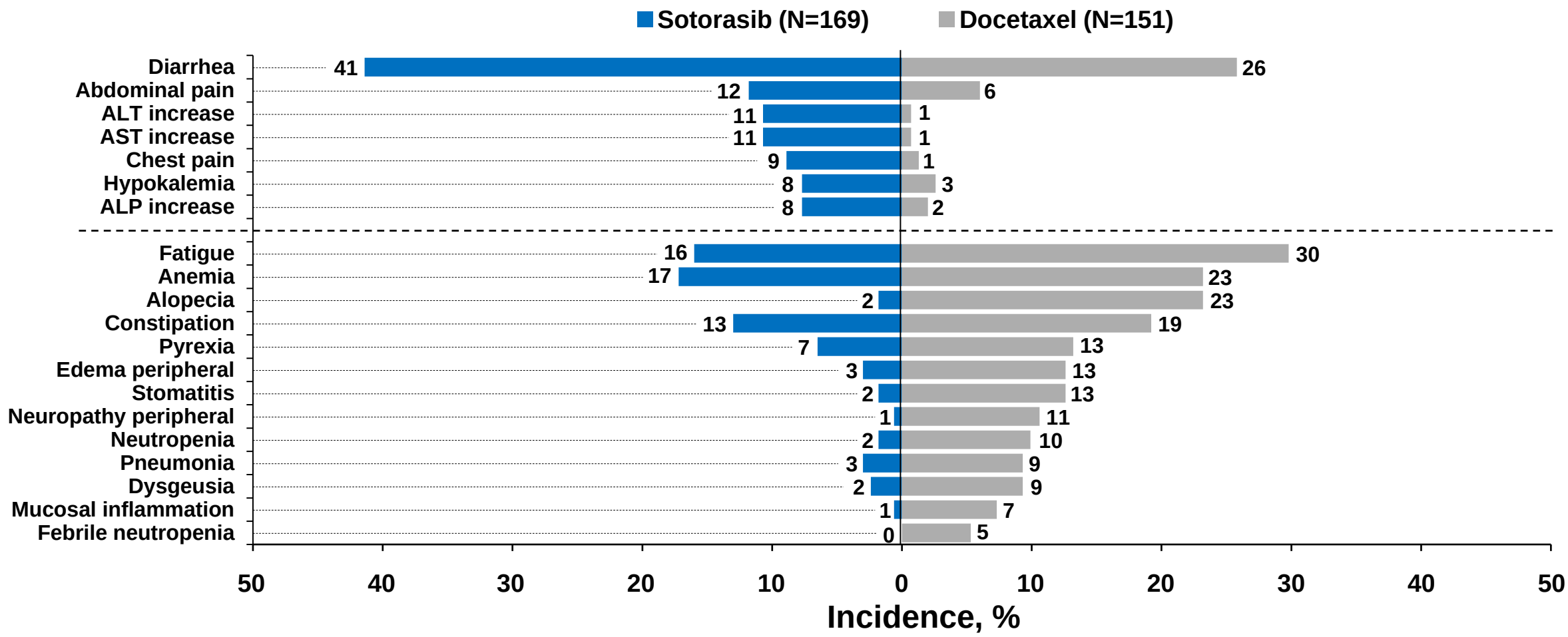
Exposure Duration

	Sotorasib N=169	Docetaxel N=151
Duration of drug administration (weeks)		
Median	**20**	**12**
Range	0.4-101	3-101
Number of cycles		
Median	**7**	**4**
Range	1-34	1-33
Relative dose intensity (%)		
Median	**100**	**95**
Range	24-100	49-106

Safety Summary



Common AEs with 5% Difference in Incidence Rate



Differentiated safety profile

Most Frequent Grade ≥3 AEs Consistent with Each Drug's Safety Profile

	Sotorasib N=169 n (%)	Docetaxel N=151 n (%)
Subjects reporting Grade ≥3 AEs	**112 (66)**	**90 (60)**
Diarrhea	**23 (14)**	4 (3)
Alanine aminotransferase increased	**14 (8)**	0
Aspartate aminotransferase increased	**10 (6)**	0
Anemia	8 (5)	**10 (7)**
Fatigue	4 (2)	**9 (6)**
Pneumonia	1 (0.6)	**9 (6)**
Neutropenia	0	**13 (9)**
Febrile neutropenia	0	**8 (5)**

Cut-off of ≥5% in either treatment group

Common AEs Leading to Treatment Modification Consistent with Each Drug's Safety Profile

	Sotorasib N=169 n (%)	Docetaxel N=151 n (%)
Leading to Treatment Modification	**93 (55)**	**67 (44)**
Diarrhea	**31 (18)**	3 (2)
Alanine aminotransferase increased	**12 (7)**	0
Aspartate aminotransferase increased	**12 (7)**	0
Fatigue	2 (1)	**10 (7)**
Pneumonia	0	**8 (5)**

Cut-off of ≥5% in either treatment group

More Hospitalizations Due to Docetaxel Toxicities

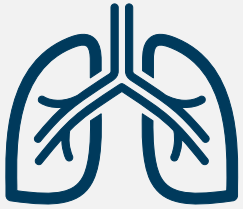
	Sotorasib N=169 n (%)	Docetaxel N=151 n (%)
Serious adverse events	**80 (47)**	**66 (44)**
Subjects reporting TEAE hospitalization	**77 (46)**	**63 (42)**
Hepatic events*	**6 (4)**	0 (0)
Diarrhea	**5 (3)**	2 (1)
Lower respiratory tract infections (pneumonia)*	1 (0.6)	**13 (9)**
Breathing abnormalities (dyspnea)*	2 (1)	**7 (5)**
Neutropenia*	0	**7 (5)**
Anemia	1 (0.6)	**5 (3)**
Sepsis*	0	**5 (3)**
Subjects reporting TRAE hospitalization	**15 (9)**	**33 (22)**

Cut-off ≥3% in either treatment group.
* Grouped AE terms.

Sotorasib Key Risks

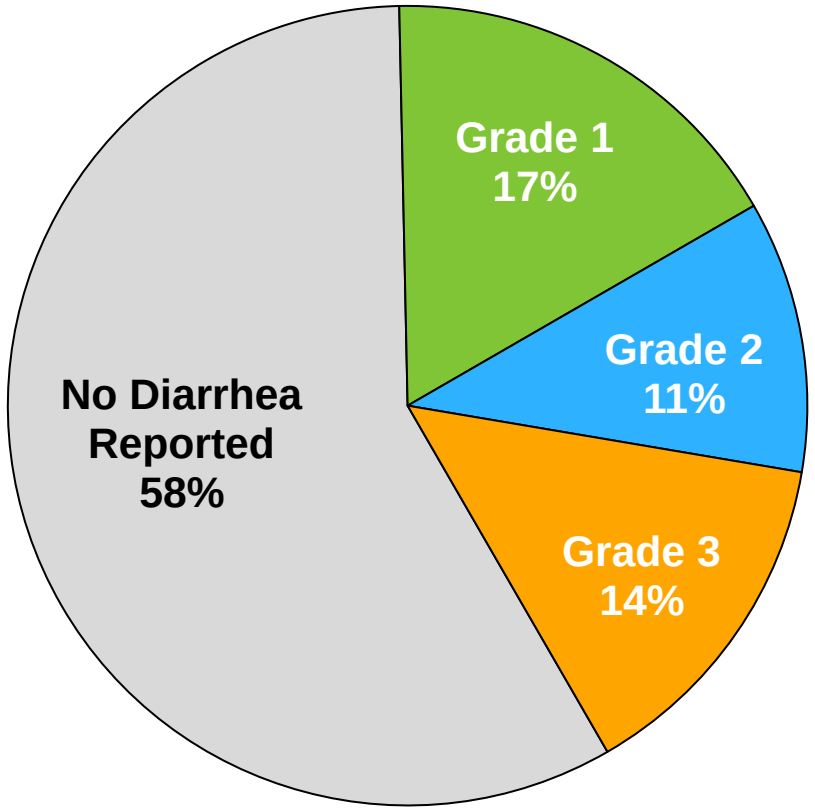
Diarrhea

Hepatotoxicity



Interstitial lung disease

Diarrhea – Manageable with Dose Modifications and Anti-Diarrheals

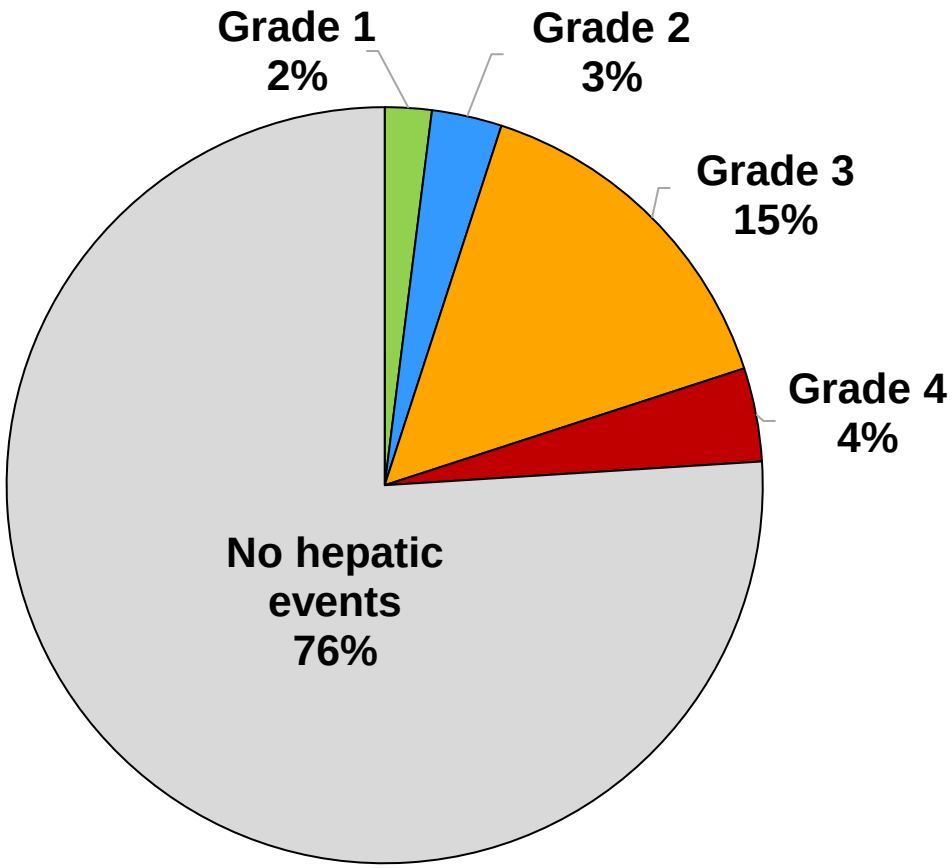


	Sotorasib N=169
Diarrhea, N1 (%)	70 (41)
Management	
Dose interruption	26 (15)
Dose reduction	14 (8)
Discontinuation	1 (0.6)
Antidiarrheals, n/N1	53 (76)
Outcome	
With fully resolved events*, n/N1	57 (81)
Median duration of events, all grades (days)	22

*Unresolved diarrhea reported in 13 patients:
8 patients died from DP; diarrhea events resolved after SFU in 2 patients; 1 patient withdrew consent; 1 patient completed study; and 1 patient remains on active treatment.

Hepatic Events Due to Lab Abnormalities

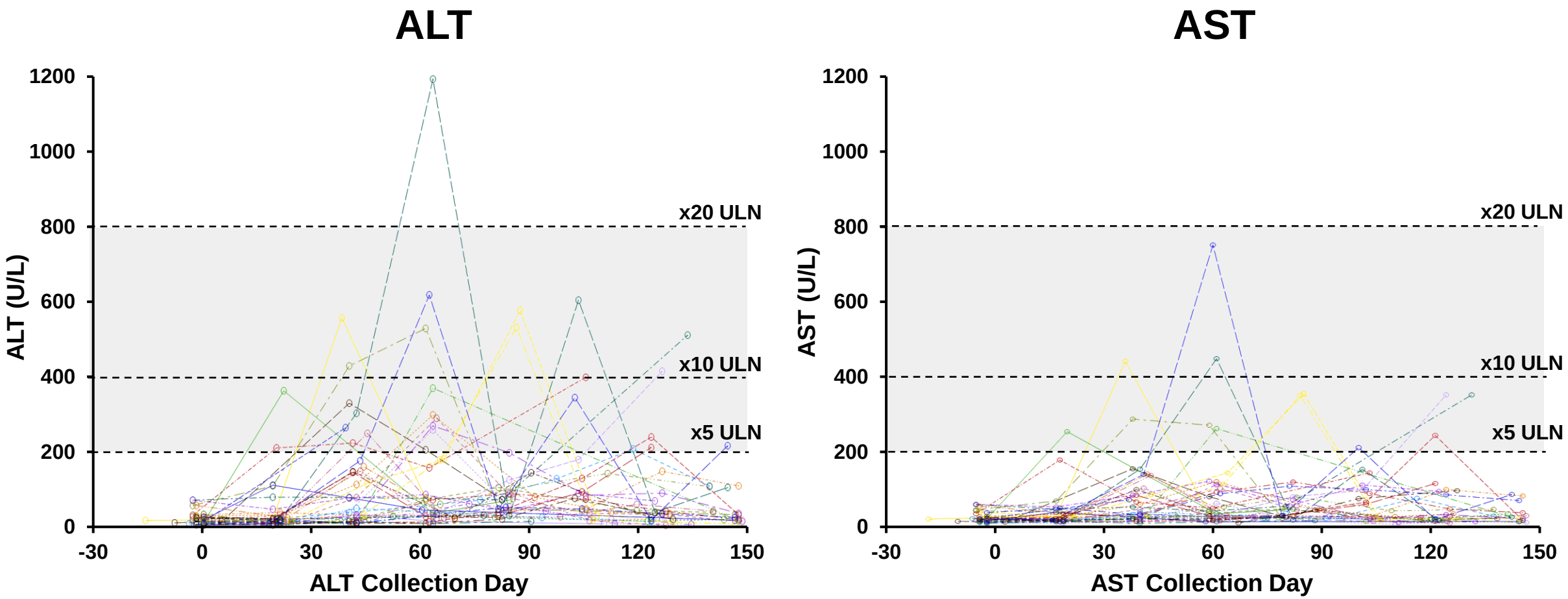
Frequent (n≥3) events	Sotorasib N=169
Hepatotoxicity EOI, n (%)	**41 (24)**
ALT increased	18 (11)
AST increased	18 (11)
GGT increased	5 (3)
Blood bilirubin increased	5 (3)
Hepatic function abnormal	3 (2)
Hypertransaminasemia	3 (2)



No reports of severe* or fatal liver injury

*Based on DILI severity index

Patients on Sotorasib With ALT or AST >3x ULN (N=39)



ALT/AST elevations reversible and responsive to treatment modification

Hepatic AEs – Manageable with Dose Modifications and Steroids

	Sotorasib N=169
Hepatotoxicity, N1 (%)	**41 (24)**
Management	
Dose interruption	30 (18)
Dose reduction	11 (7)
Discontinuation	13 (8)
Corticosteroids, n/N1 (%)	28 (68)
Outcomes	
Subjects with fully resolved events*, n/N1 (%)	36 (88)
Median duration of events, all grade (days)	22

*Unresolved hepatic events reported in 5 subjects:
3 subjects died from disease progression prior to event resolution; 1 subject lost to follow-up; 1 subject discontinued sotorasib due to hepatic AE and no further information reported.

PRO: Sotorasib Patients Less Bothered by Side Effects

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

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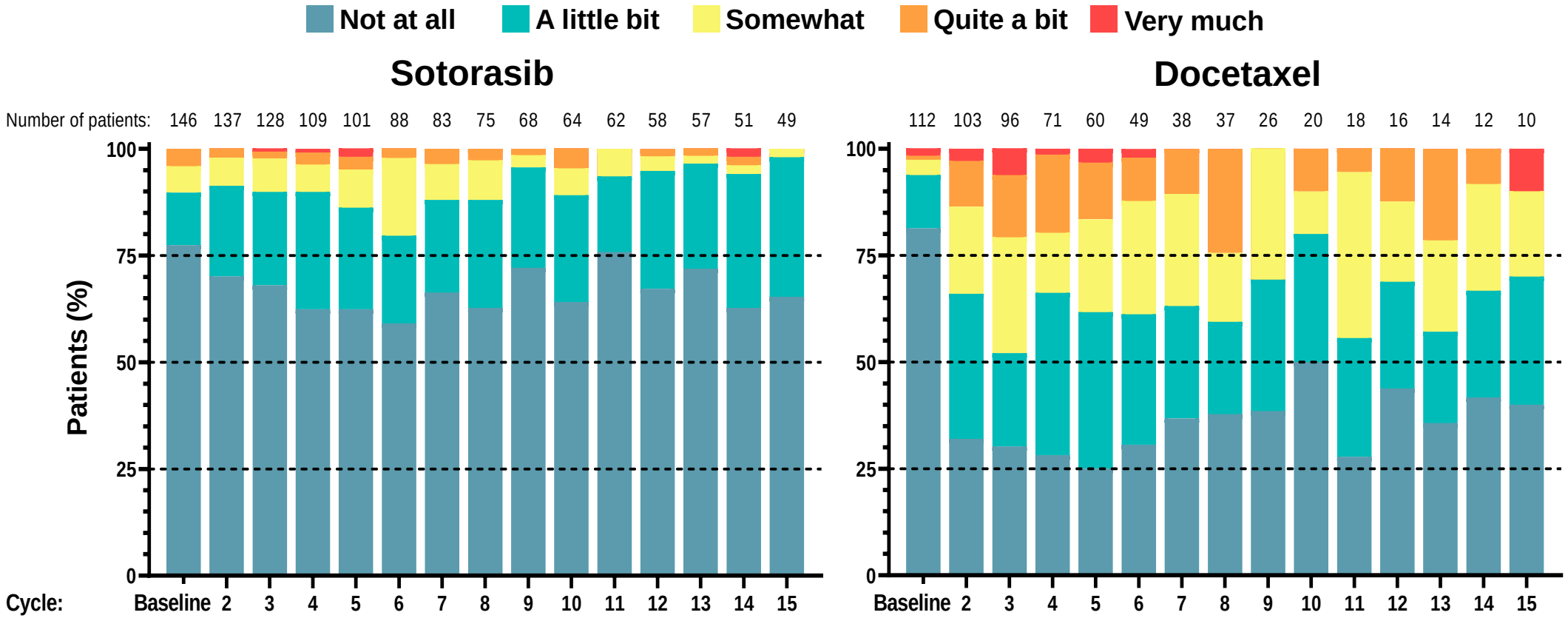
FACT-G GP5: "I am bothered by side effects of treatment"



OR = 5.71; 95% CI 2.98-10.91

Overall Safety Conclusions

- **Safety profile of sotorasib is consistent with its established profile**
- **Differentiated safety profile**
- **Patients on sotorasib report being less bothered by side effects**
- **Key risks can be managed by appropriate monitoring, dose modifications, and supportive care**

Reliability of CodeBreaK 200 Results

Gregory Friberg, MD

Vice President, Medical Affairs

Amgen Inc.

An Adequate and Well-Controlled Trial Should Include

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

Pages 11 and 12 of FDA briefing document

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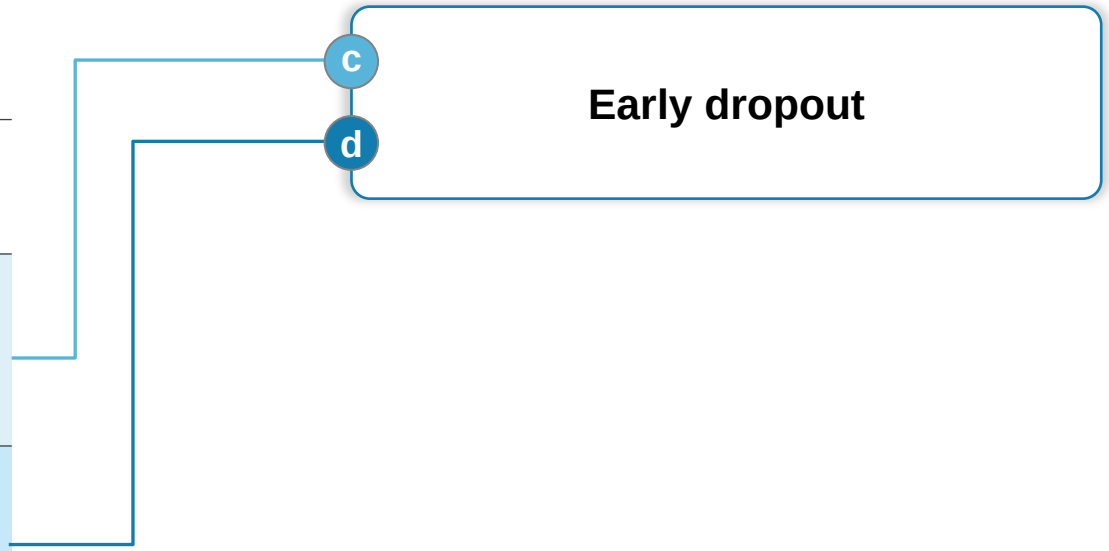

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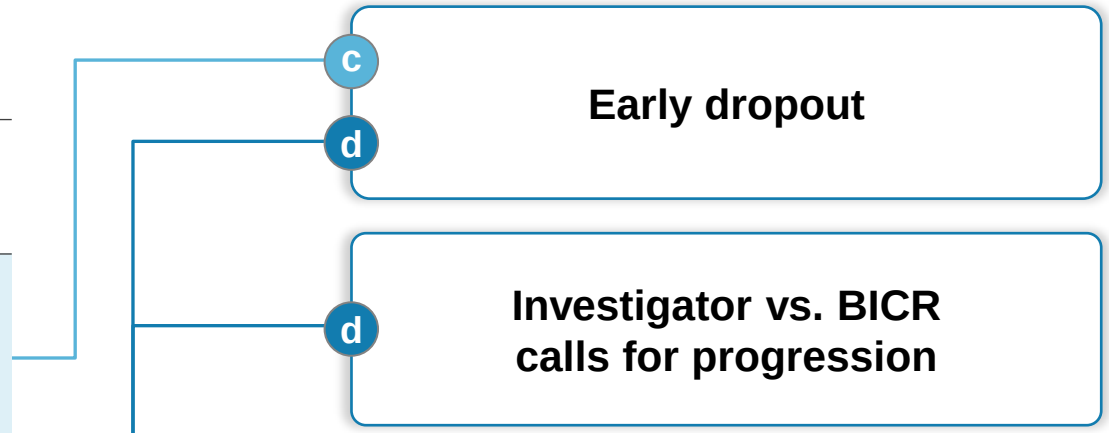

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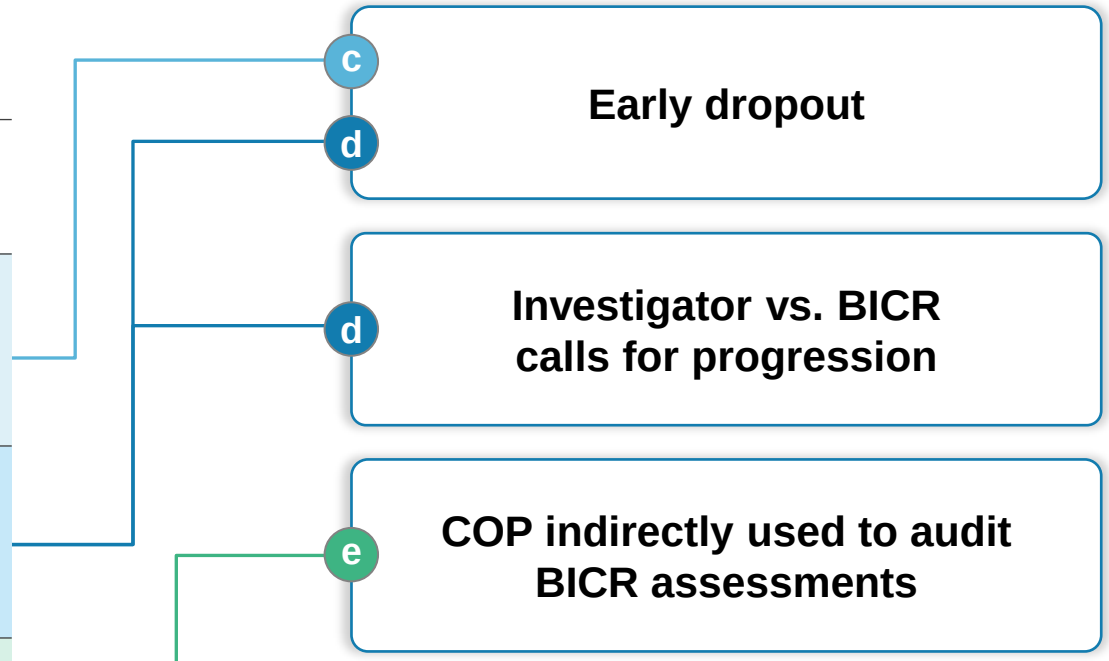

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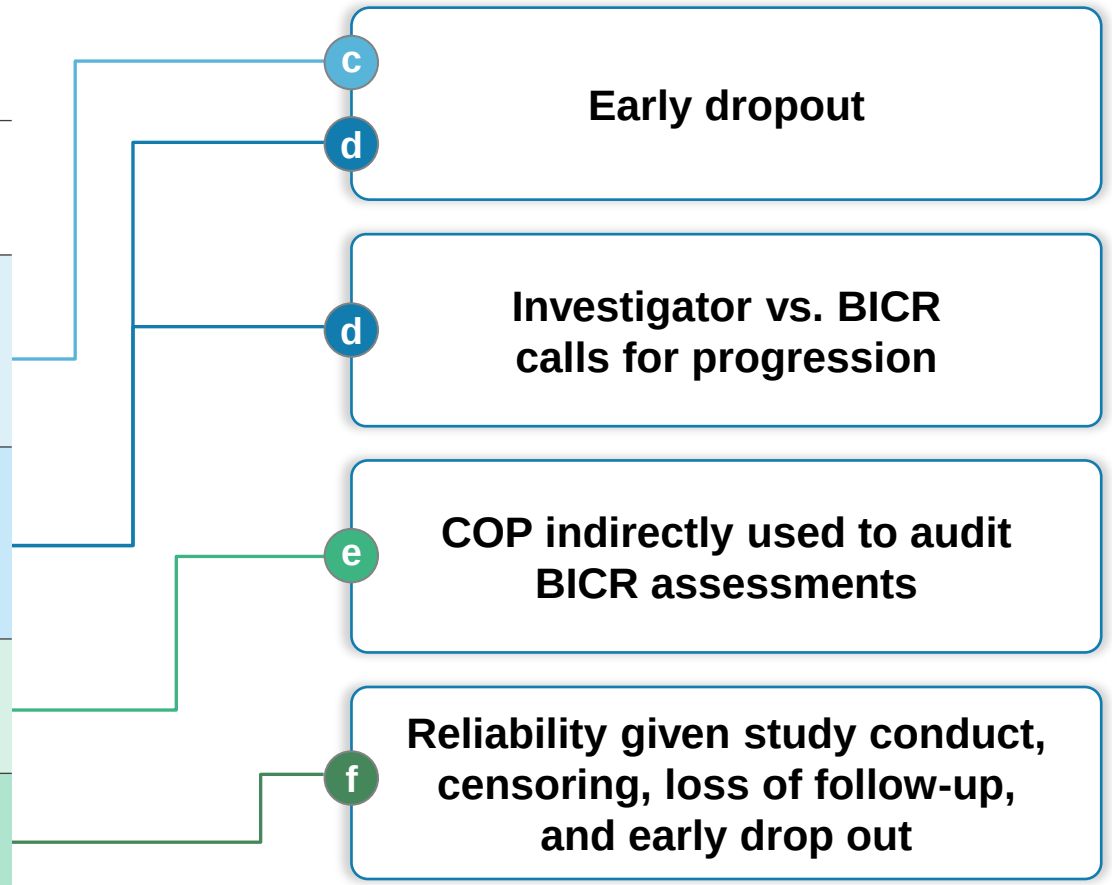

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Addressing Potential Sources of Bias

c d	Early dropout	Clinical characteristics	Covariate adjusted Cox model	Imputation methods

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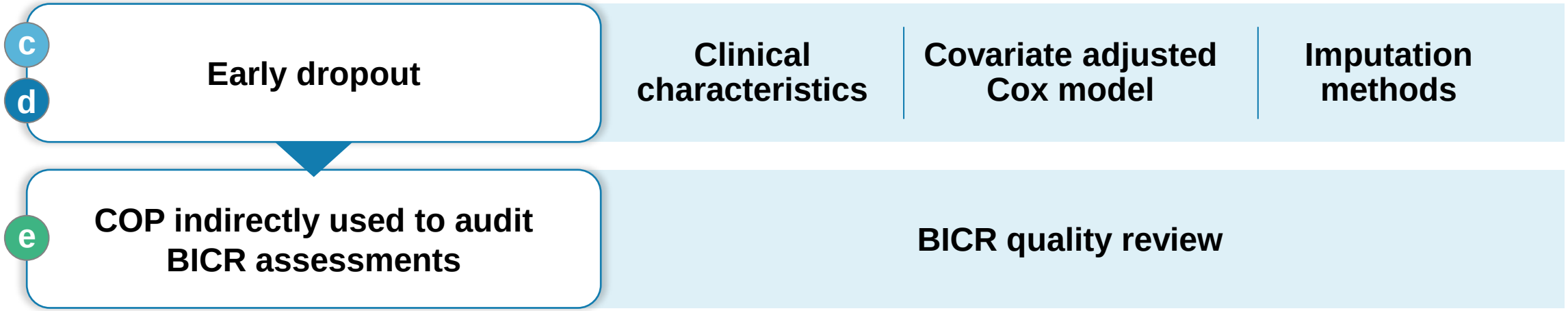

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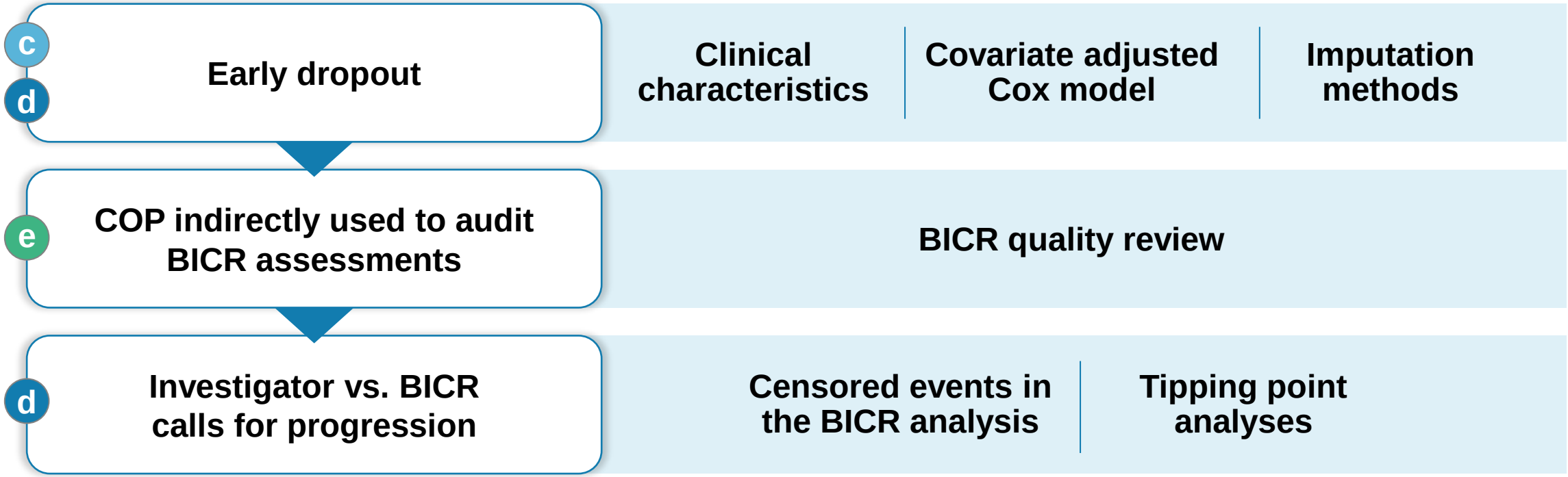

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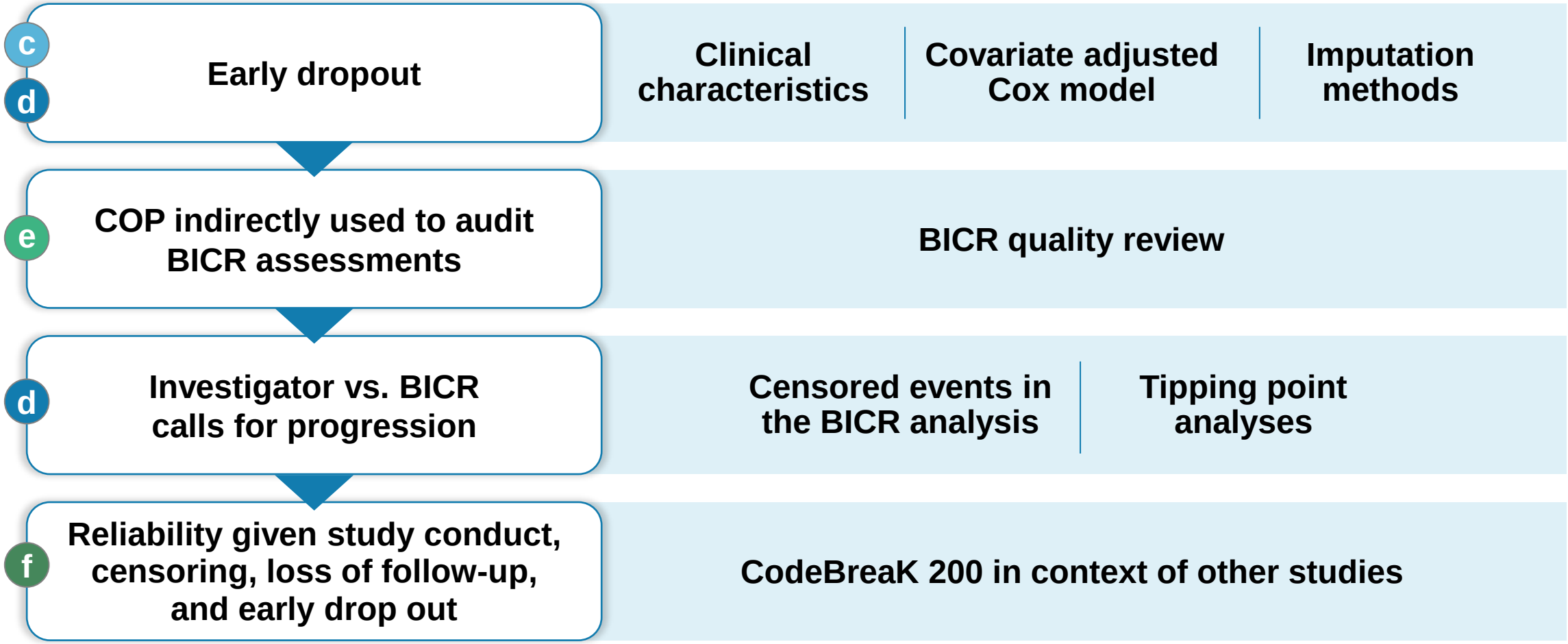


Untreated Early Dropout in the Docetaxel Arm

	Docetaxel Untreated N=23	Docetaxel Treated N=151
Age, years, median (range)	67 (54, 87)	64 (35, 81)
North America / Europe / Other, %	13 / 70 / 17	13 / 73 / 15
Smoking history (current or former)	21 (91)	145 (96)
ECOG performance status 1	**17 (74)**	**98 (65)**
History of CNS involvement	**10 (43)**	**50 (33)**
Liver metastasis	**7 (30)**	**28 (19)**
Prior lines of therapy		
1	11 (48)	67 (44)
2	8 (35)	61 (40)
>2	4 (17)	23 (15)
Tumor burden by SLD, > median	10 (44)	74 (49)

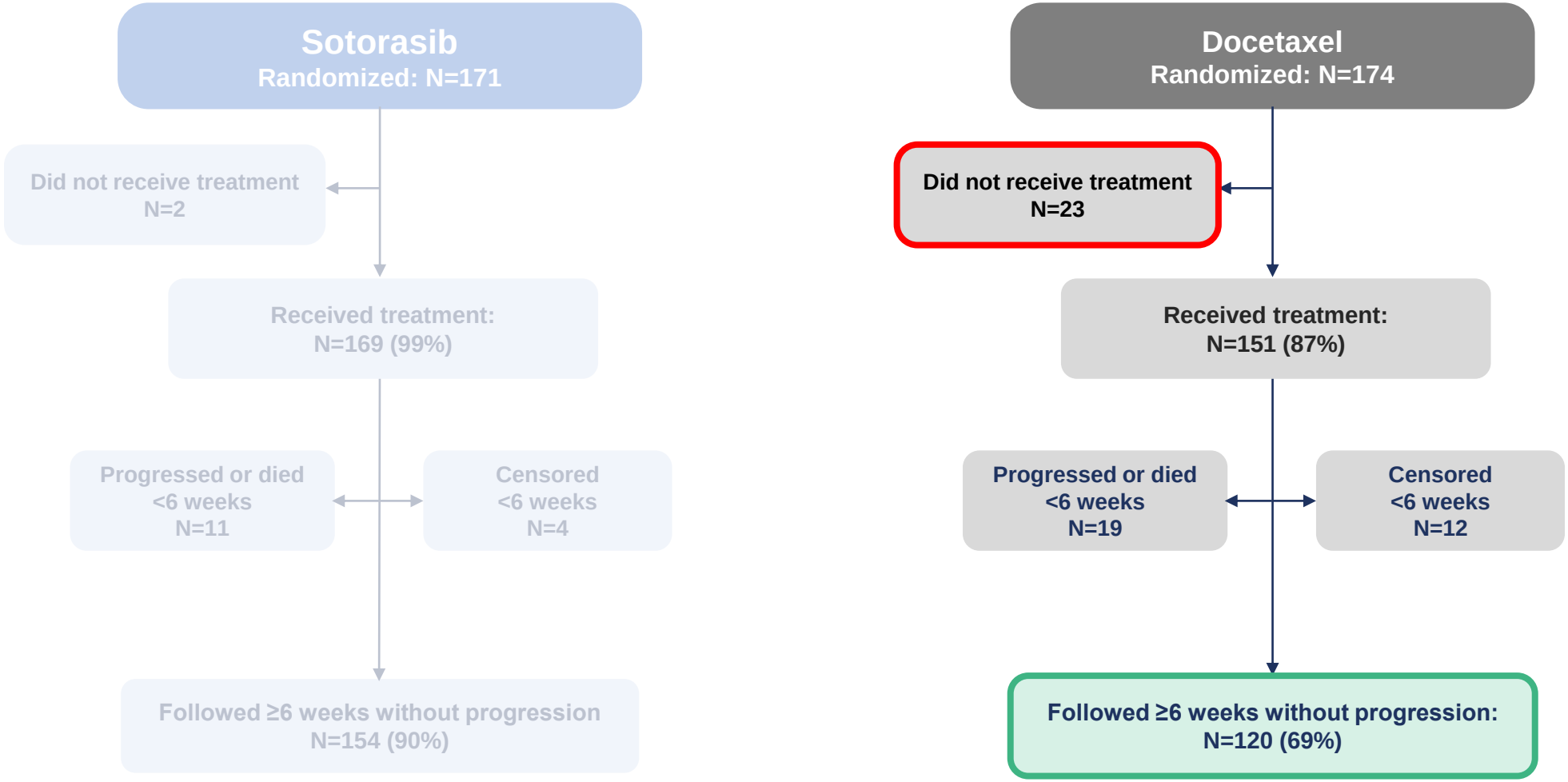
Untreated Early Dropout: Covariate-Adjusted PFS Analysis Supports Primary Results

Stratified Cox Model
Adjusted for Additional Covariates

Sotorasib vs Docetaxel HR (95% CI)	Descriptive p-value
0.60 (0.46, 0.79)	<0.001

- **Additional covariates with ≥10% prevalence**
  - Liver metastasis (yes, no)
  - Baseline tumor burden (>median, ≤median)
  - ECOG performance status (0,1)
  - Age (<, ≥65)
  - North America (yes, no)
- **Stratification factors**
  - Prior lines of therapy (1, 2, >2)
  - History of CNS involvement (yes, no)
  - Race (Asian vs Non-Asian)

Simulations to Address Untreated Early Dropouts on Docetaxel



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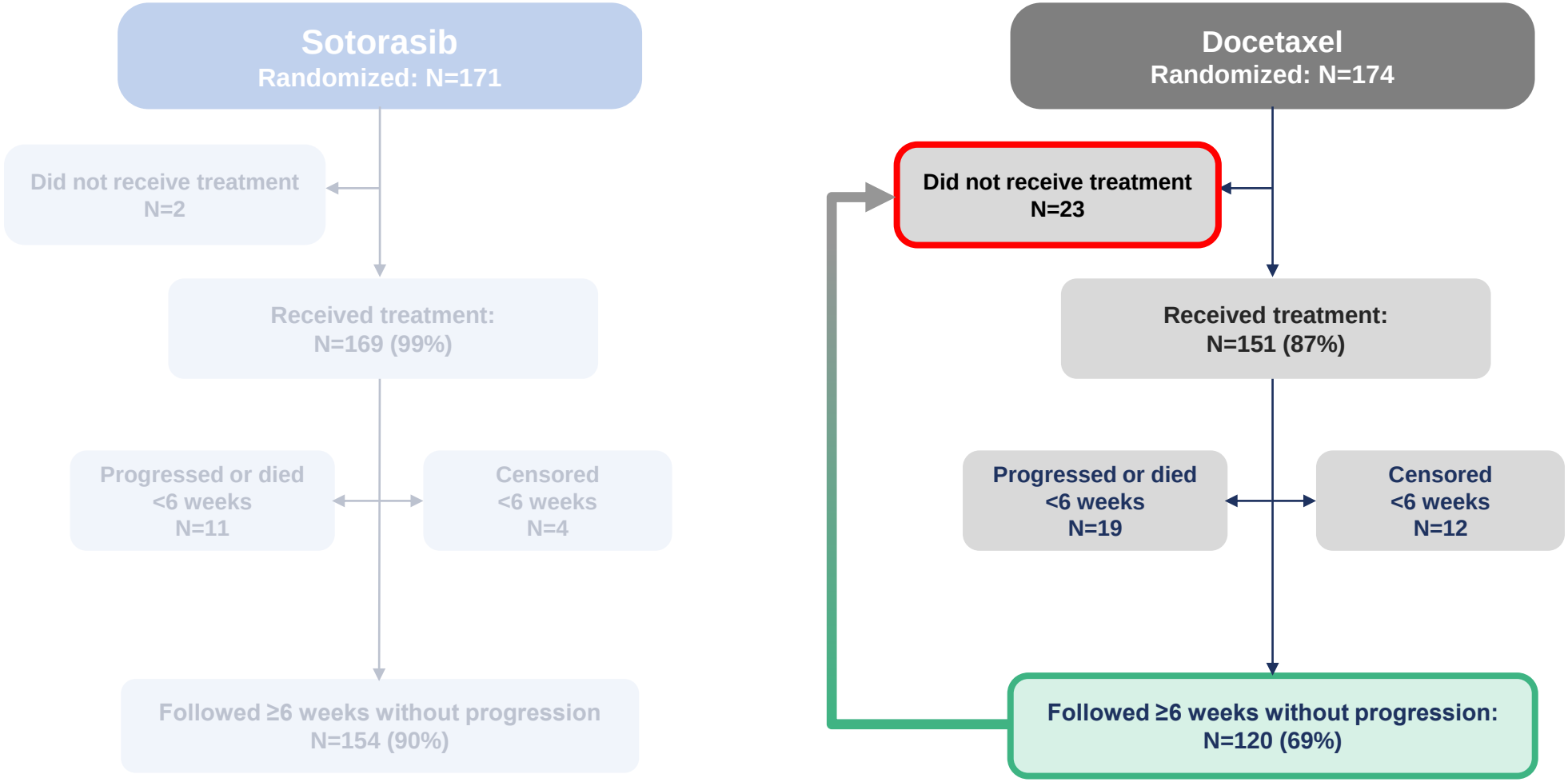


Untreated Early Dropout: PFS Imputation Results Support Primary Analysis

Based on 20,000 Simulations

Imputed Patients by Resampling	Average HR (95% CI)	Proportion of Times Sotorasib PFS Advantage was Statistically Significant
23 untreated in docetaxel	**0.70** (0.54, 0.90)	99.1%

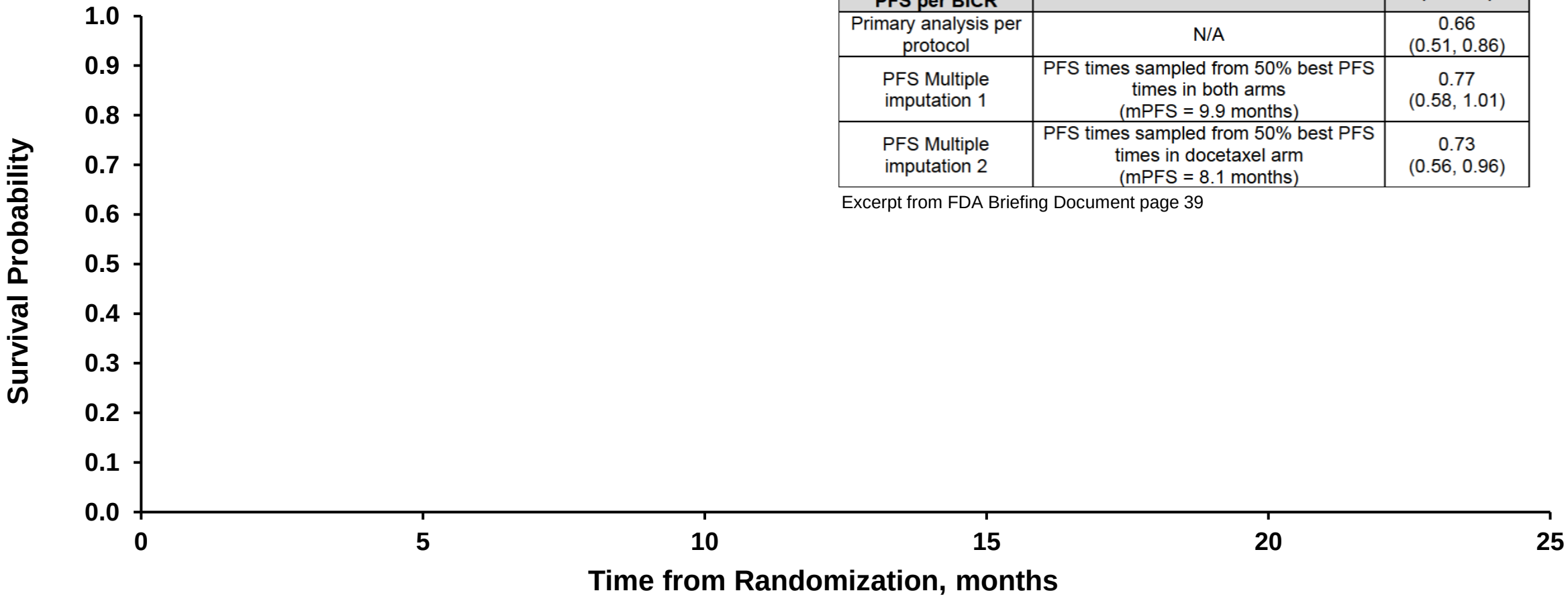
- **For 23 docetaxel untreated patients, resampling was performed within treatment group and stratum**
- **PFS superiority threshold p<0.044**

Basis of FDA Imputation Models: Patients With Top 50% PFS Outcomes

Table 12: Sensitivity Analyses of PFS to Investigate Impact of Early Withdrawal

Sensitivity Analyses of PFS per BICR	PFS assumption for imputation	HR (95% CI)
Primary analysis per protocol	N/A	0.66 (0.51, 0.86)
PFS Multiple imputation 1	PFS times sampled from 50% best PFS times in both arms (mPFS = 9.9 months)	0.77 (0.58, 1.01)
PFS Multiple imputation 2	PFS times sampled from 50% best PFS times in docetaxel arm (mPFS = 8.1 months)	0.73 (0.56, 0.96)

Excerpt from FDA Briefing Document page 39



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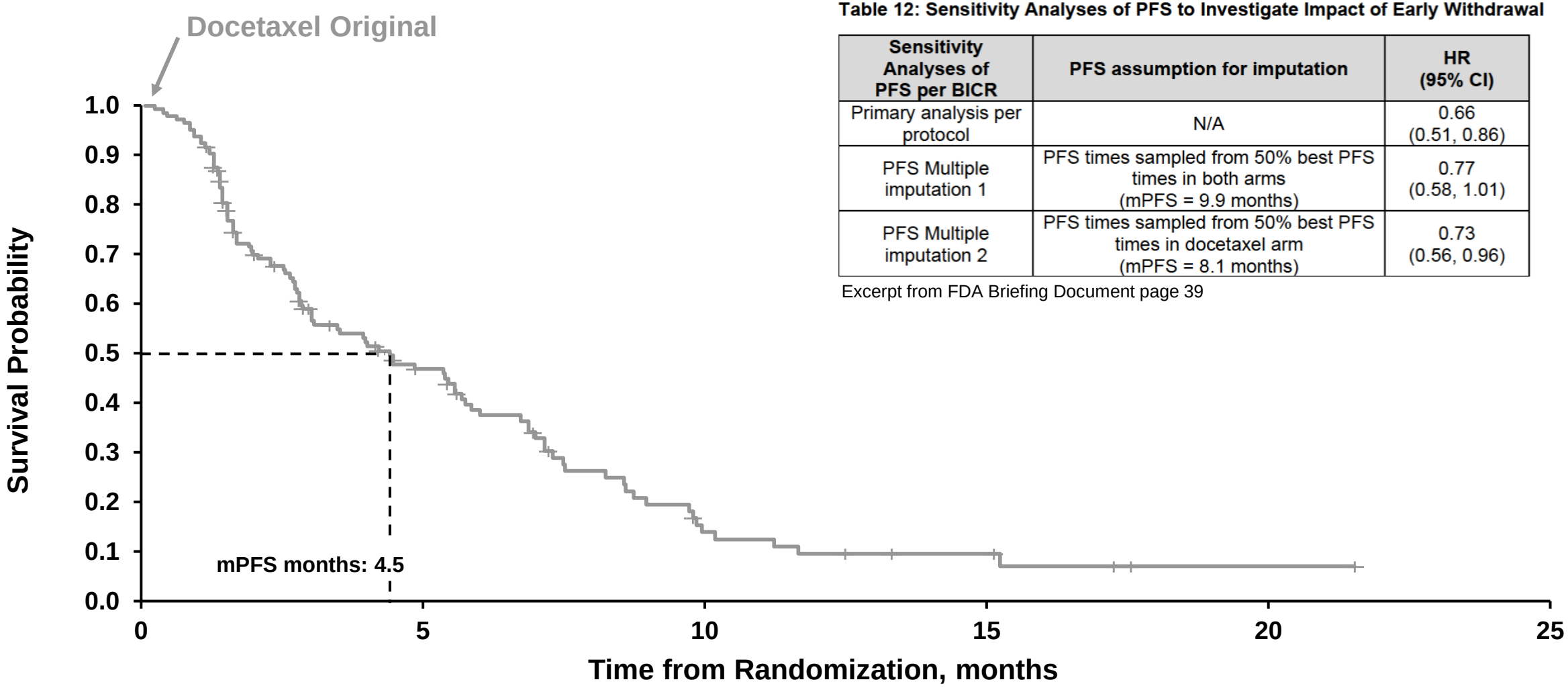

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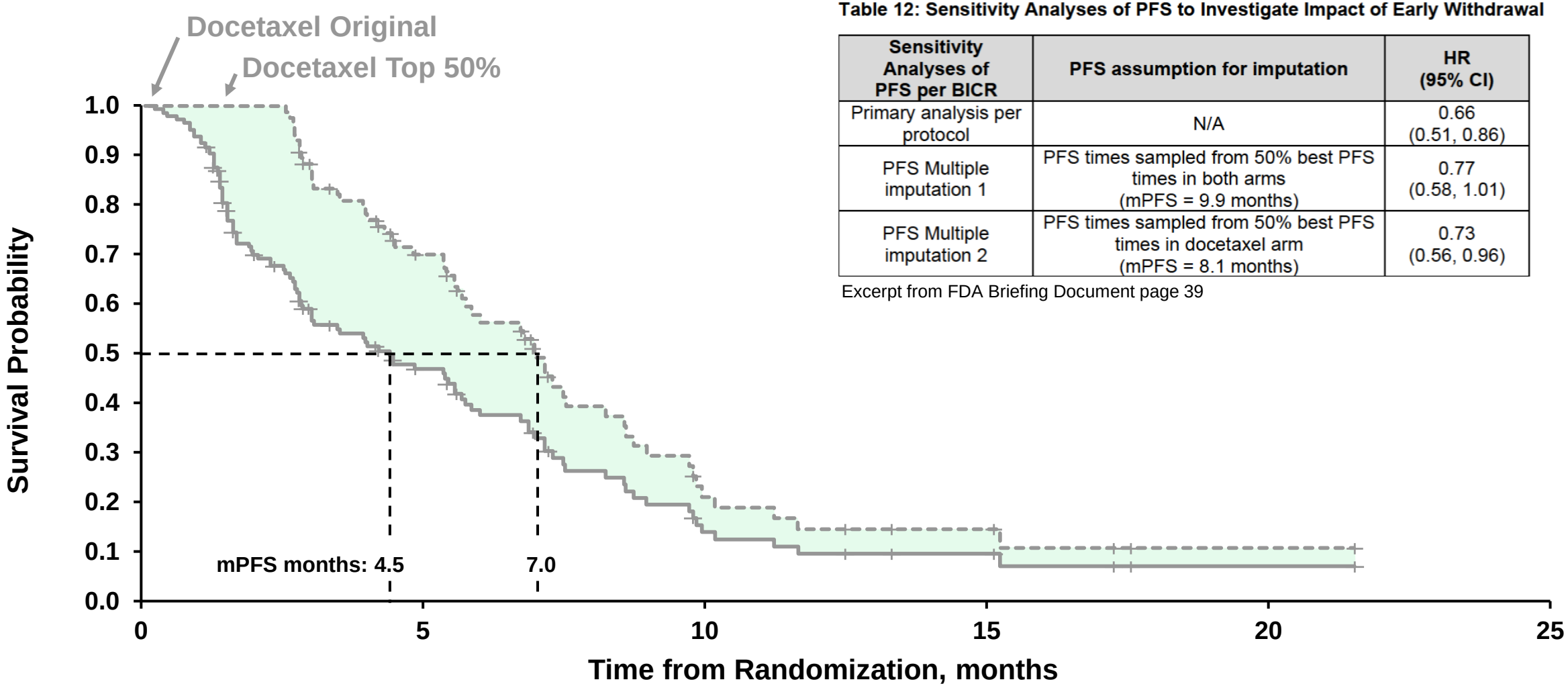

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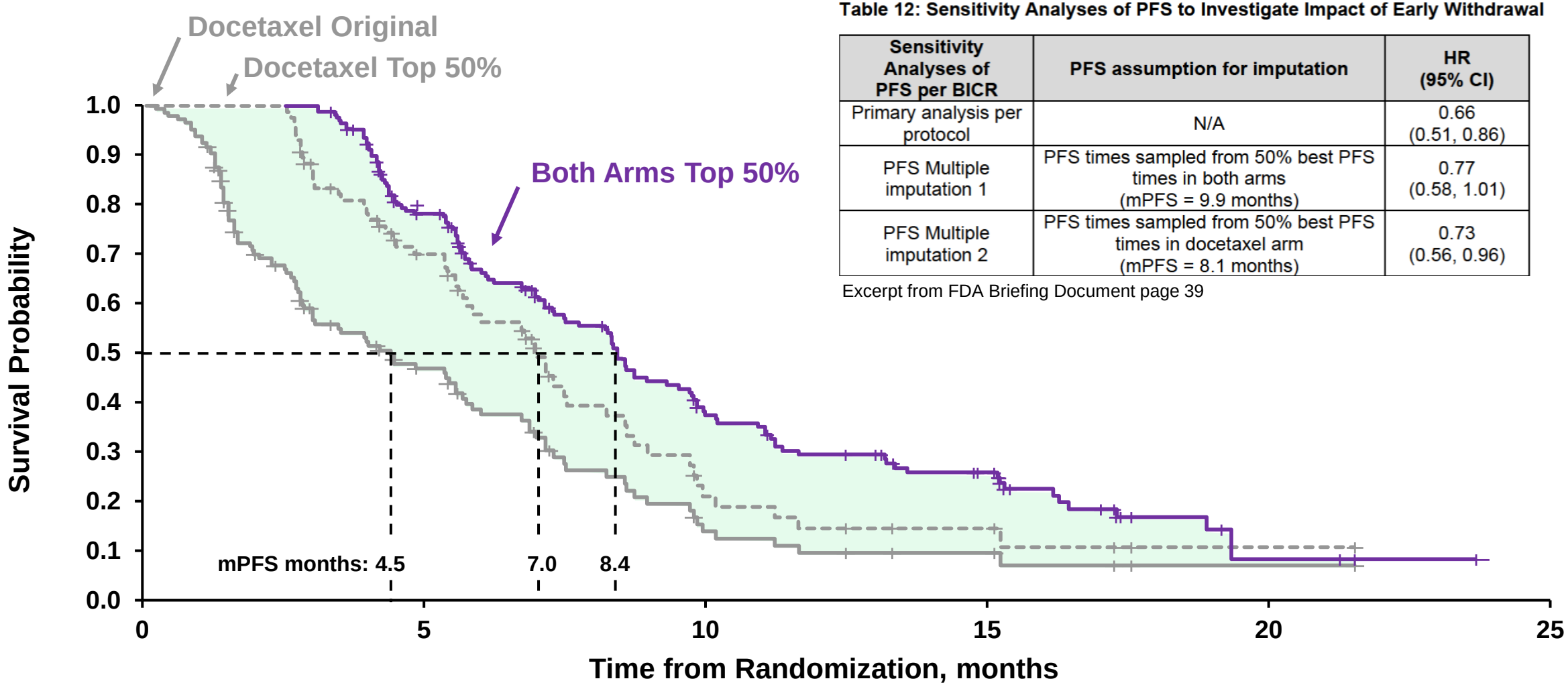

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Excerpt from FDA Briefing Document page 39

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

Censoring in BICR PFS Analysis

	Sotorasib Total Randomized: 171	Docetaxel Total Randomized: 174
BICR PFS events	**122**	**101**
BICR disease progression	100	68
Death	22	33*

*Includes 3 untreated

Censoring in BICR PFS Analysis

	Sotorasib Total Randomized: 171	Docetaxel Total Randomized: 174
BICR PFS events	**122**	**101**
BICR disease progression	100	68
Death	22	33*
BICR PFS censored	**49**	**73**
Untreated early dropout	2	20
Started new anti-cancer therapy	**24**	**31**
Other reasons	23	22

*Includes 3 untreated
Other reasons: Alive at last follow up, withdrawal of consent, discontinued treatment

Tipping Point Analysis: Therapy Switch Censoring

Sotorasib (Assumes the Worst)

All 24 censored patients called progression at start of new therapy

Docetaxel (Assumes the Best)

All 31 censored patients considered non-progressors and then called progression one by one

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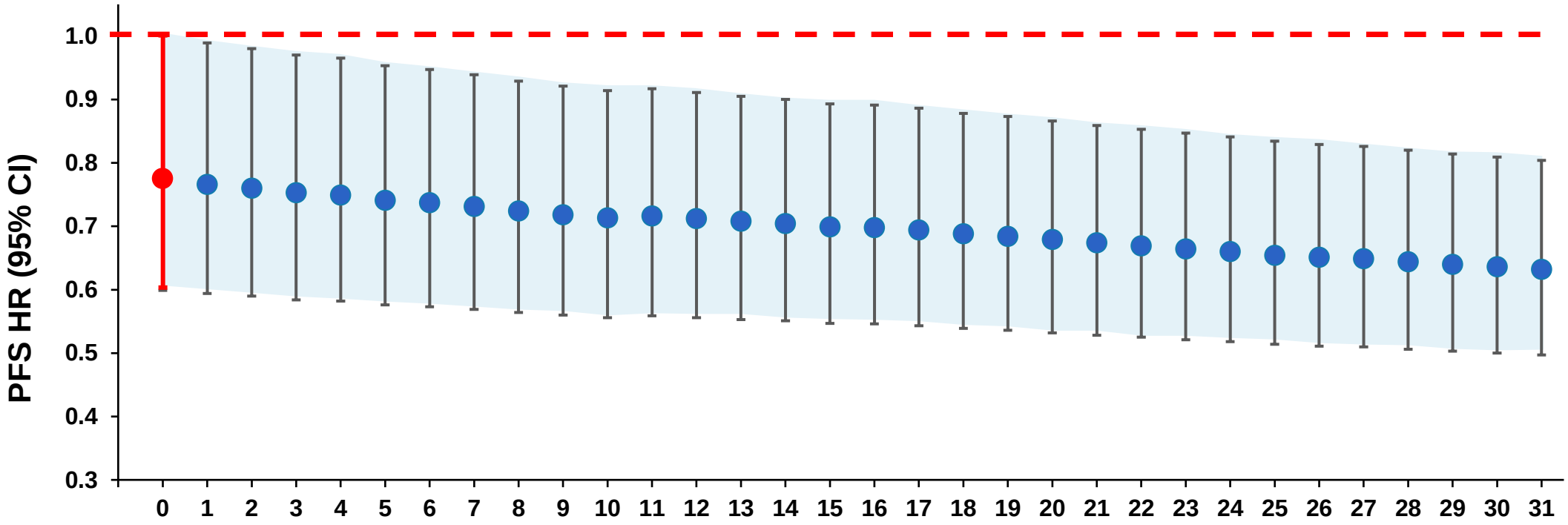

Stratified Cox model with imputed PFS events

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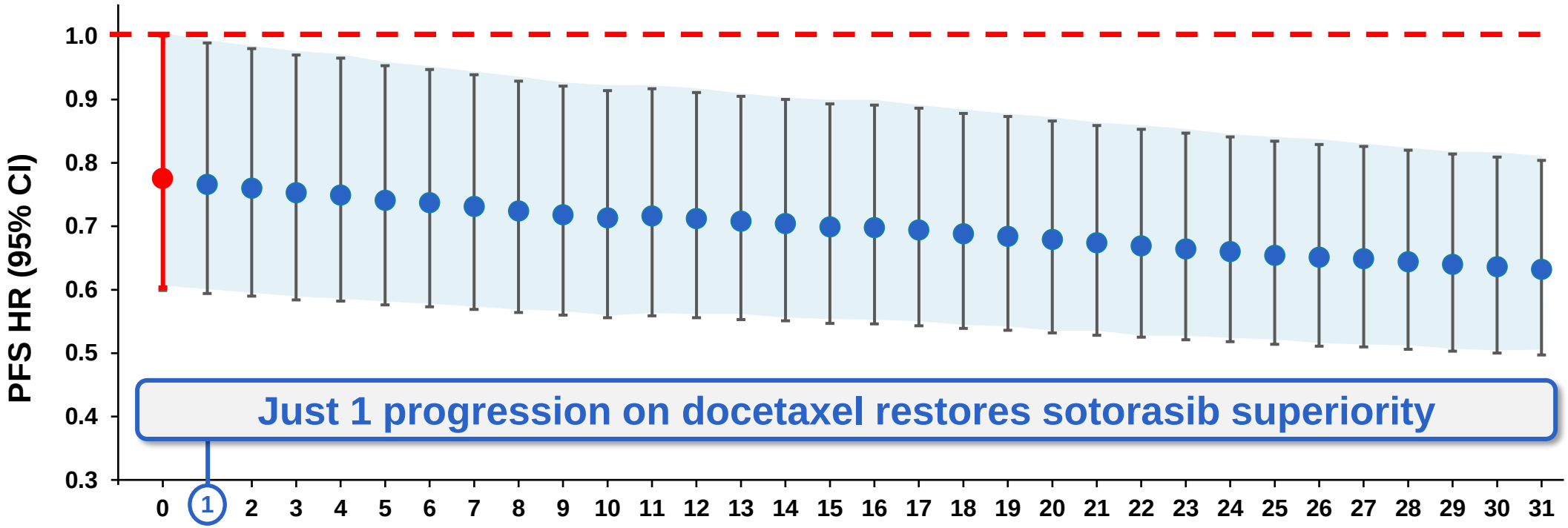

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Tipping Point Analysis: Therapy Switch Censoring and Early Dropout

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Docetaxel (Assumes the Best)

All 31 therapy switches and 20 untreated early dropouts considered non-progressors and then called progression one by one

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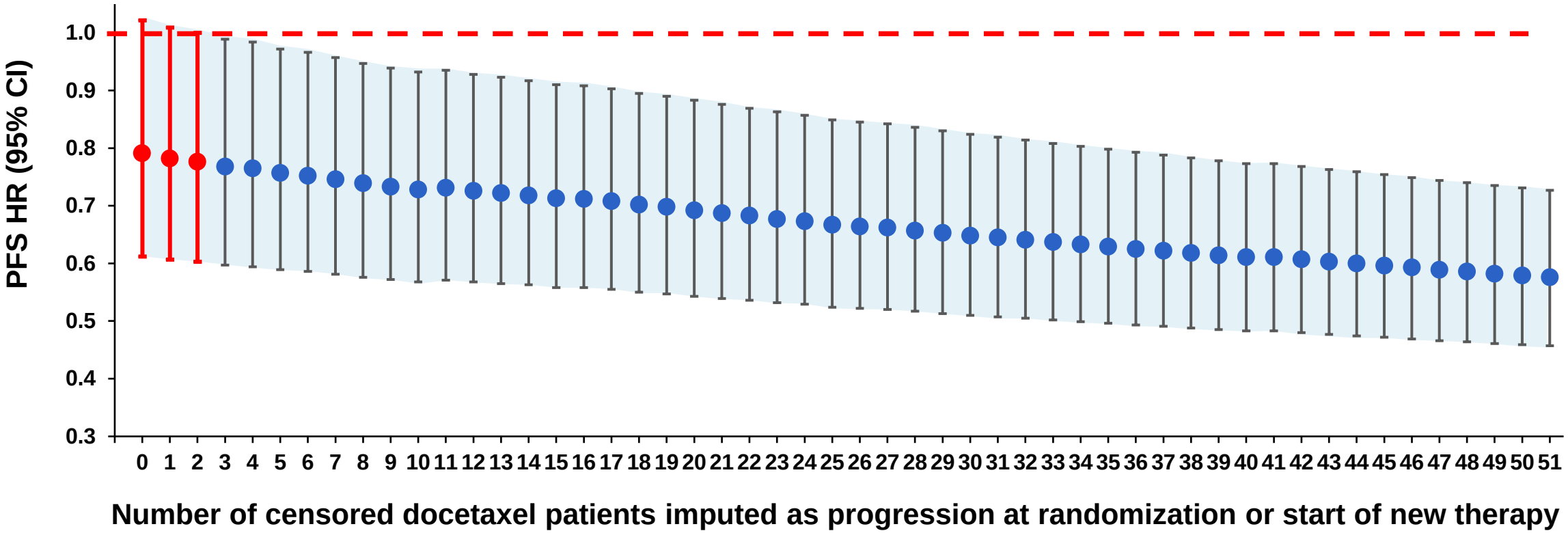


Stratified Cox model with imputed PFS events

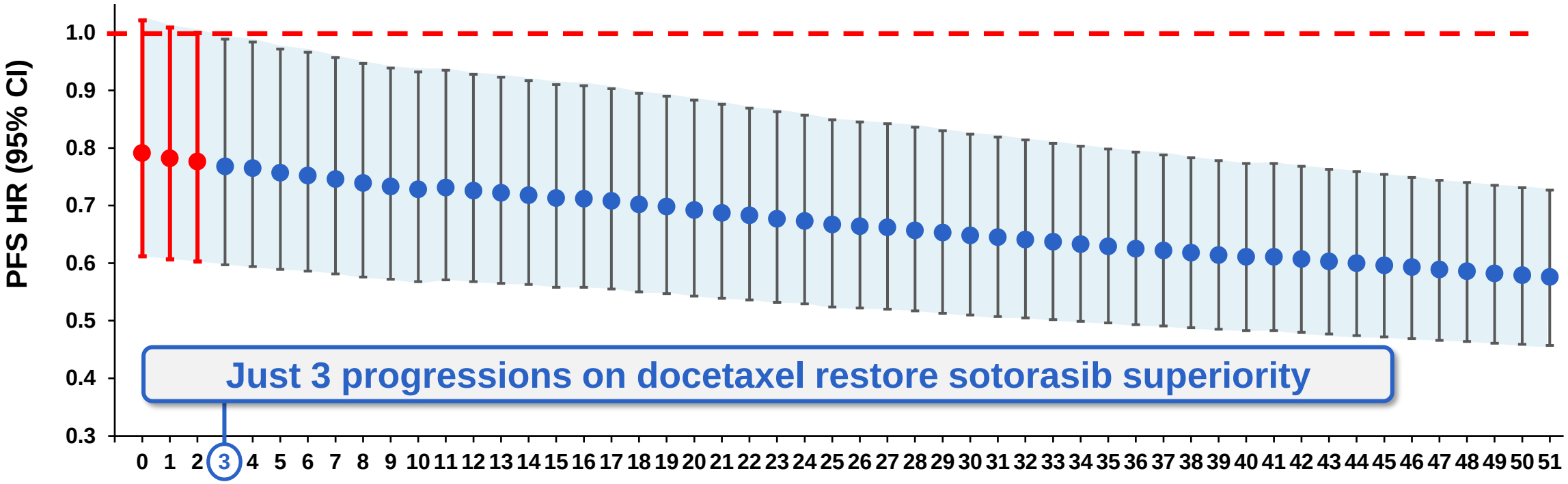
Tipping Point Analysis: Therapy Switch Censoring and Early Dropout

Sotorasib (Assumes the Worst)

All 24 therapy switches called progression at switch and 2 untreated early dropouts called progression at randomization

Docetaxel (Assumes the Best)

All 31 therapy switches and 20 untreated early dropouts considered non-progressors and then called progression one by one



Stratified Cox model with imputed PFS events

CodeBreaK 200 Results Consistent With Other Studies

	Sotorasib CB 100 N=126	Sotorasib Dose Comparison N=104	CodeBreaK 200 Sotorasib CB 200 N=171	CodeBreaK 200 Docetaxel CB 200 N=174	Docetaxel CM 057[1] N=209	Docetaxel REVEL[2] N=625	Docetaxel CONTACT-01[3] N=180
ORR	37%	33%	**28%**	**13%**	12%	13.6%	13.3%
Median PFS	6.8 mo	5.4 mo	**5.6 mo**	**4.5 mo**	4.2 mo	3.0 mo	4.0 mo
Median OS	12.5 mo	13.0 mo	**10.6 mo**	**11.3 mo**	9.4 mo	9.1 mo	10.5 mo

CB=CodeBreaK

1. Borghaei, H., et al. (2015). *The New England Journal of Medicine*, 373(17), 1627–1639.
2. Garon, E. B., et al. (2014) *Lancet* (London, England), 384(9944), 665–673.
3. Neal J, et al. (2023). European Lung Cancer Congress 2023, Abstract 6O

Clinical Perspective

Melissa Johnson, MD

Director of Lung Cancer Research,
Sarah Cannon Research Institute

While Outcomes for Patients with Advanced NSCLC Have Improved, the Majority of Patients Progress on 1L Therapy Within a Year[1]

- **ICI-based regimens have become the 1L SoC**
- **1 of 5 patients will be alive at five years**
- **Over 50% of patients progress after the first year, regardless of 1L therapy**

1L=first-line, ICI=immune checkpoint inhibitor, SoC=standard of care

1. Garassino MC, et al. *J Clin Oncol*. 2023.

While Outcomes for Patients with Advanced NSCLC Have Improved, the Majority of Patients Progress on 1L Therapy Within a Year[1]

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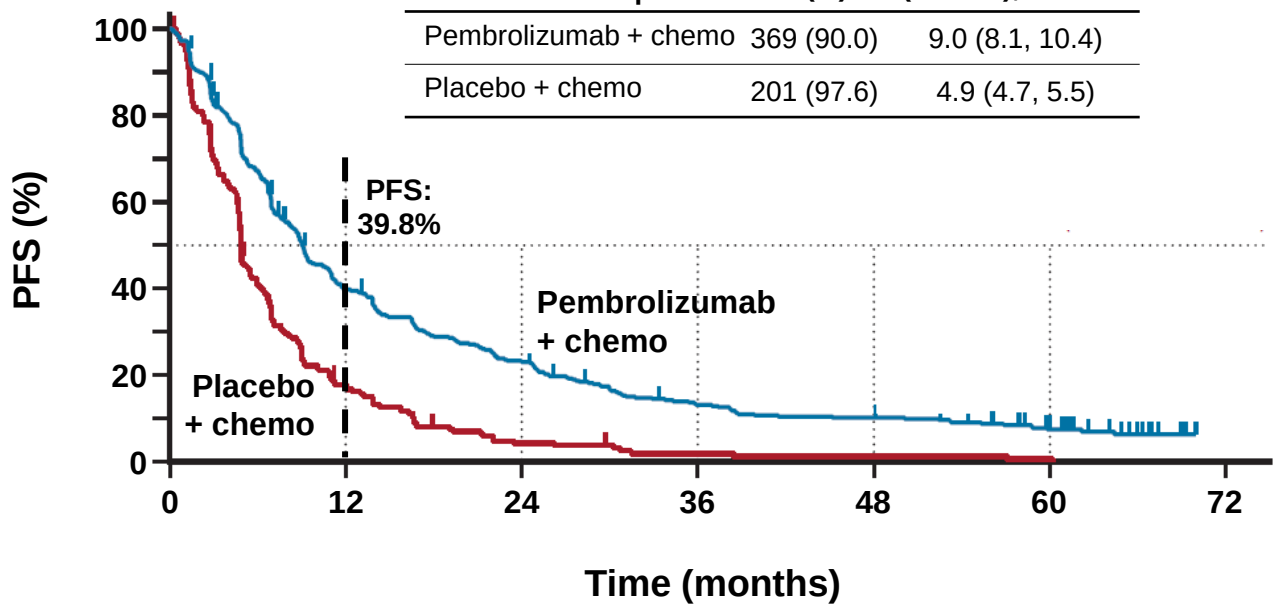
KEYNOTE-189: Pembrolizumab + Chemotherapy in 1L mNSCLC[1]

Treatment Group	Events n (%)	Median (95% CI), months
Pembrolizumab + chemo	369 (90.0)	9.0 (8.1, 10.4)
Placebo + chemo	201 (97.6)	4.9 (4.7, 5.5)



1L=first-line, ICI=immune checkpoint inhibitor, SoC=standard of care, PFS=progression-free survival, mNSCLC=metastatic non-small cell lung cancer

1. Garassino MC, et al. *J Clin Oncol*. 2023.

Second-Line Treatment Options for Immunotherapy-Experienced Patients Remain Limited

NCCN Recommended 2L Options[1]
(ICI-exposed)

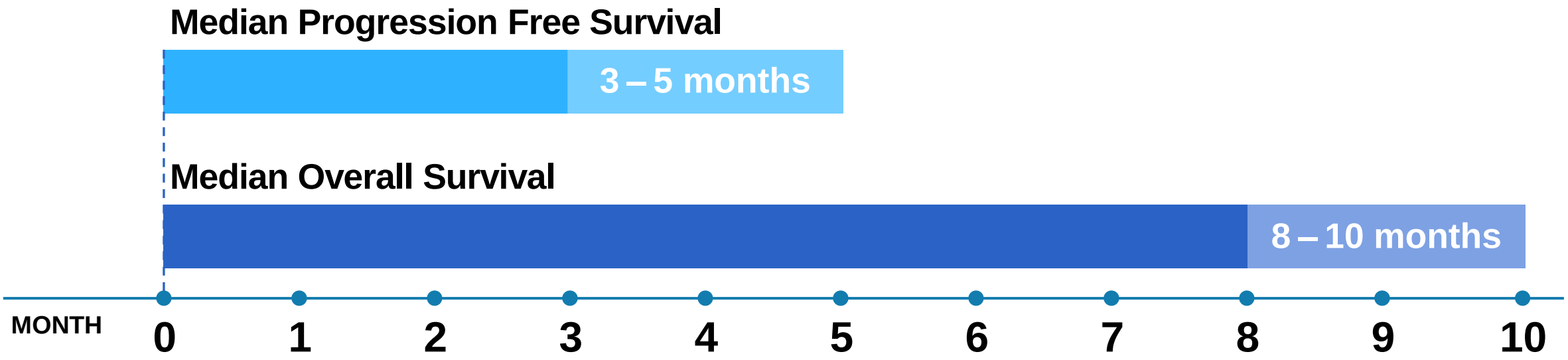
- **Docetaxel** → **60-70%** of 2L treatment[2]
- **Pemetrexed**
- **Gemcitabine**
- **Ramucirumab/docetaxel**
- **Albumin-bound paclitaxel**

Chemotherapy remains the backbone of 2L NSCLC therapy in ICI-exposed patients with or without *KRAS p.G12C* mutations

NCCN=National Comprehensive Cancer Network, 2L=second-line,
1. NCCN NSCLC Guidelines V2.2023; 2. Amgen Data on File

Docetaxel is an Active Agent and Has Been SoC for 2L mNSCLC for >20 Years

Efficacy from Previous Trials with Docetaxel



Objective Response Rate = **10-15%**

Borghaei H, et al. *N Engl J Med*. 2015.; Garon EB, et al. *Lancet*. 2014.; Rittmeyer A, et al. *Lancet*. 2016.

Docetaxel Patient Experience Remains Suboptimal

- **Dosing and administration**
  - One-hour intravenous infusion
  - 75 mg/m^2, every 3 weeks
  - Dose reductions are common
  - 3 days of steroid administration is common

FEBRILE NEUTROPENIA
Hospitalization risk

STOMATITIS

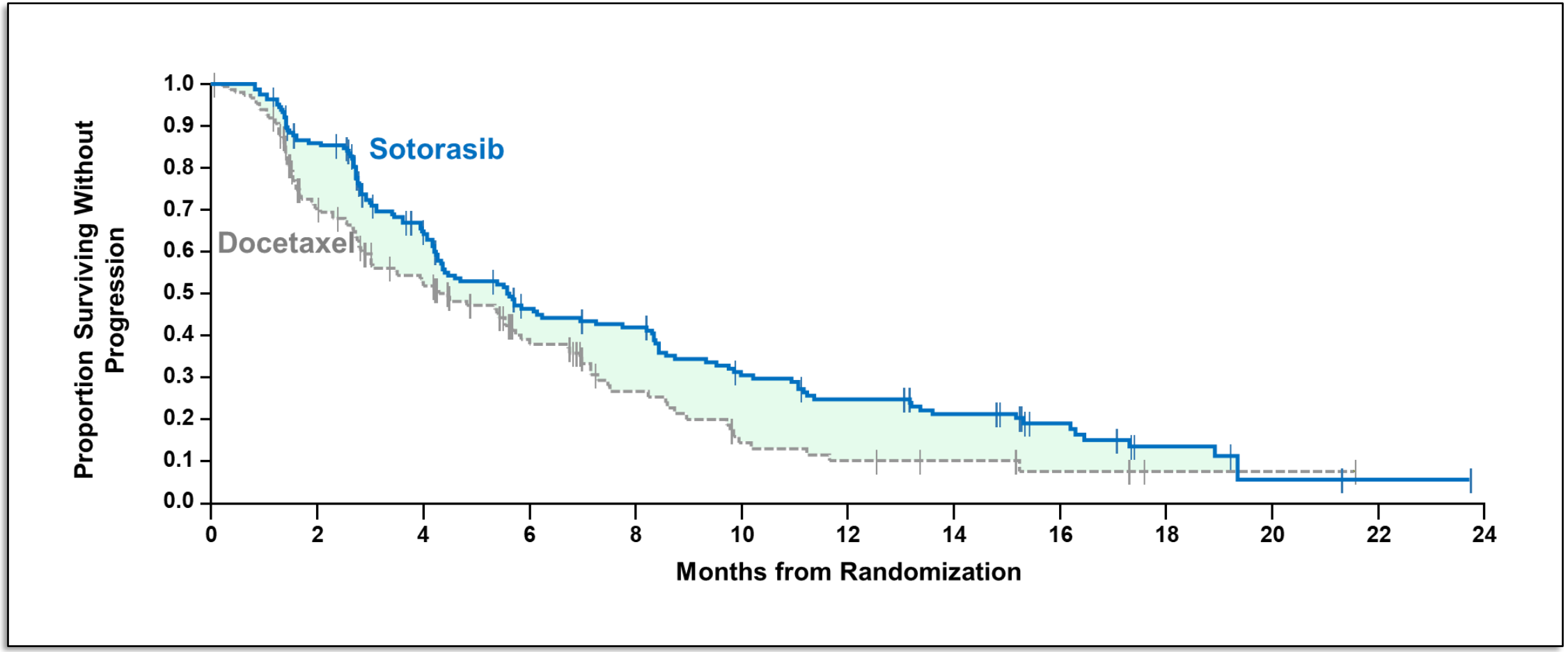
ALOPECIA

NAIL CHANGES

Taxotere Prescribing Information.

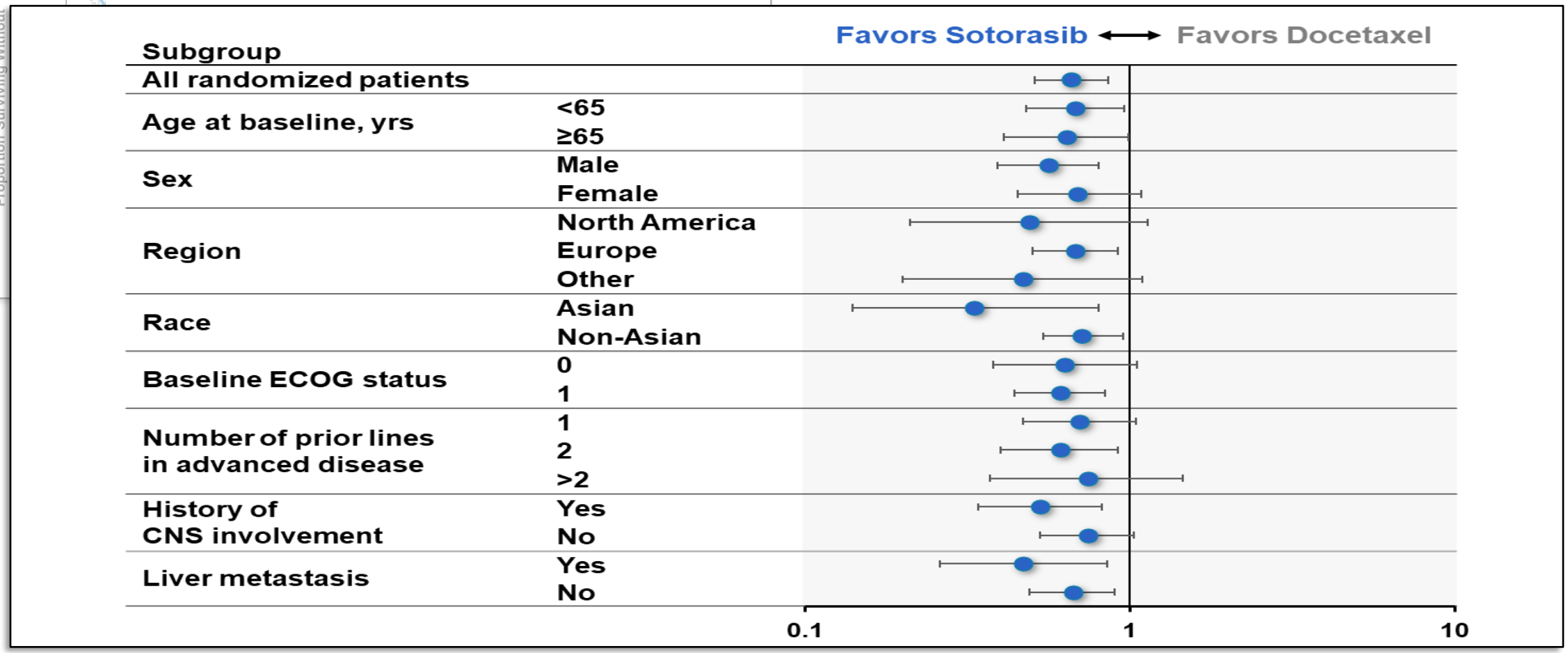
Sotorasib Demonstrated Meaningful Efficacy Benefits Compared to Docetaxel

Progression Free Survival



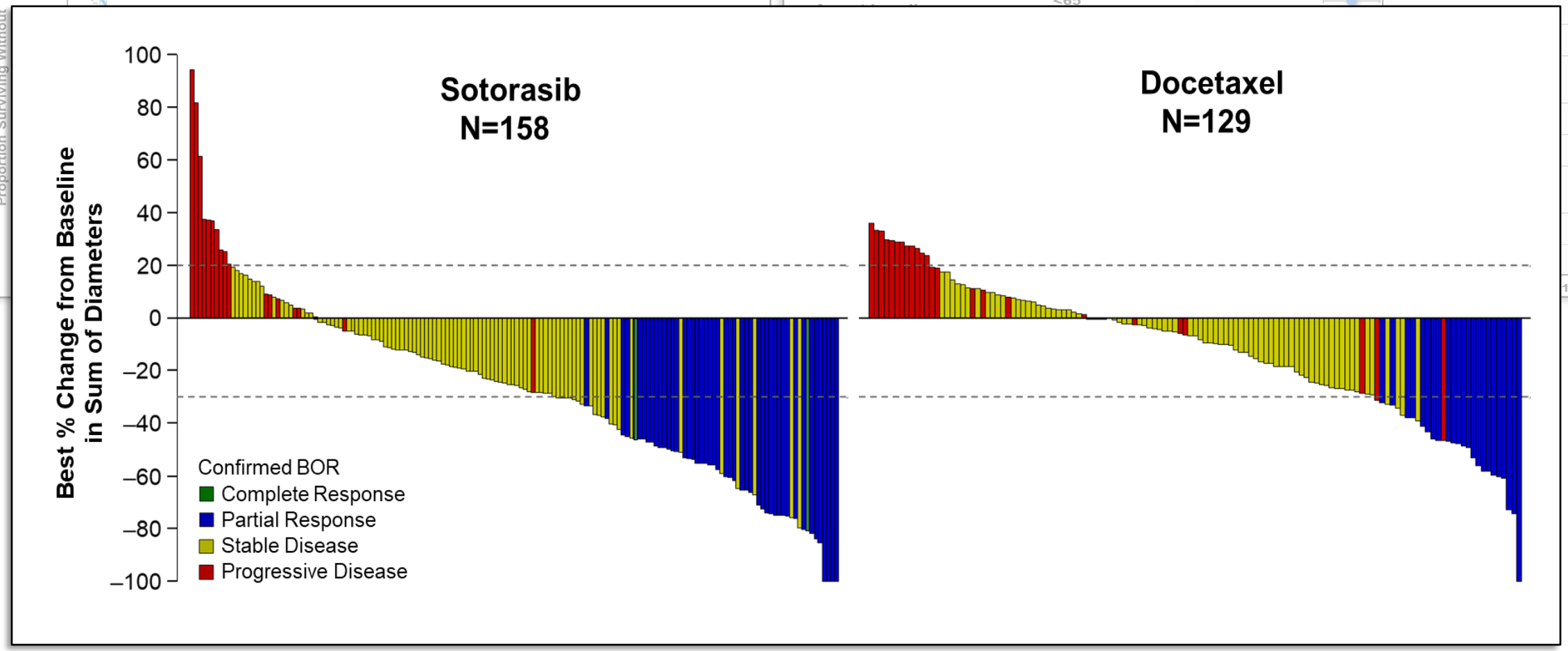
Sotorasib Demonstrated Meaningful Efficacy Benefits Compared to Docetaxel

Progression Free Survival Forest Plot



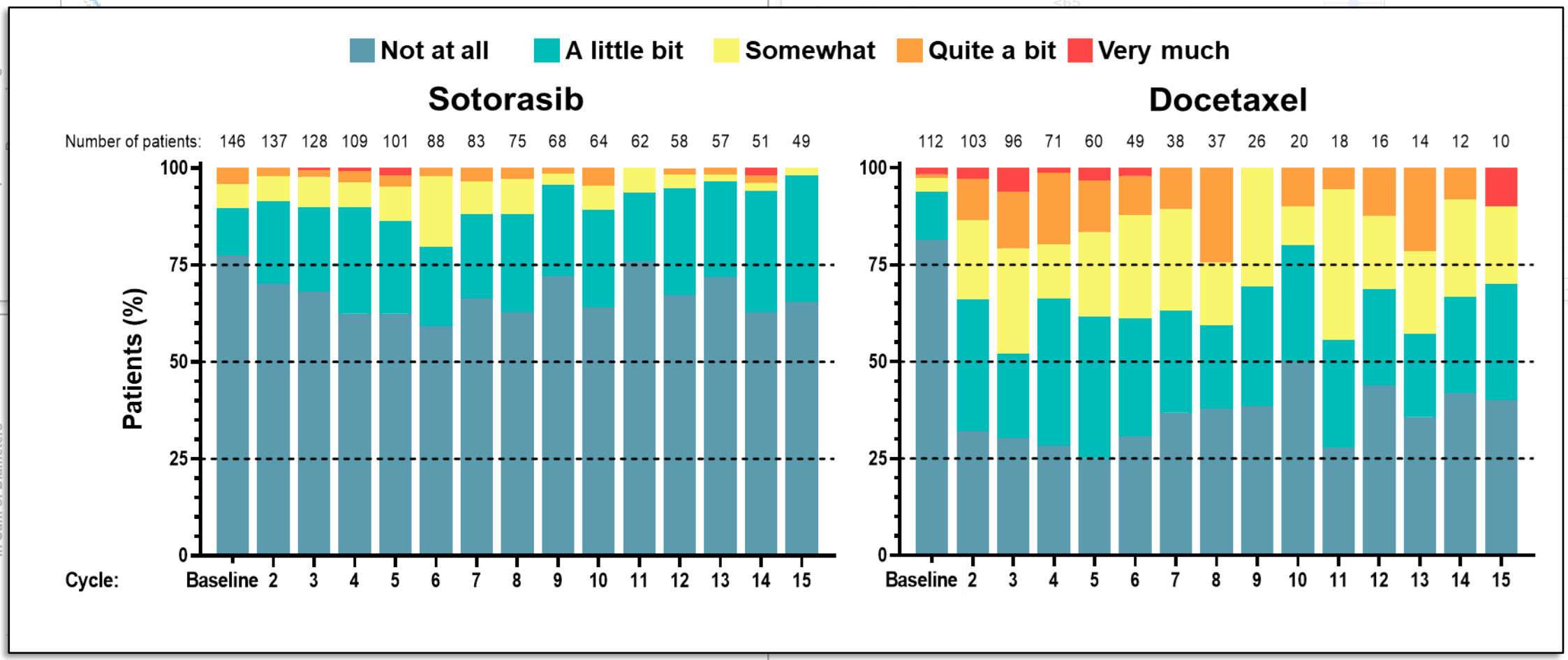
Sotorasib Demonstrated Meaningful Efficacy Benefits Compared to Docetaxel

Response Waterfall Plot

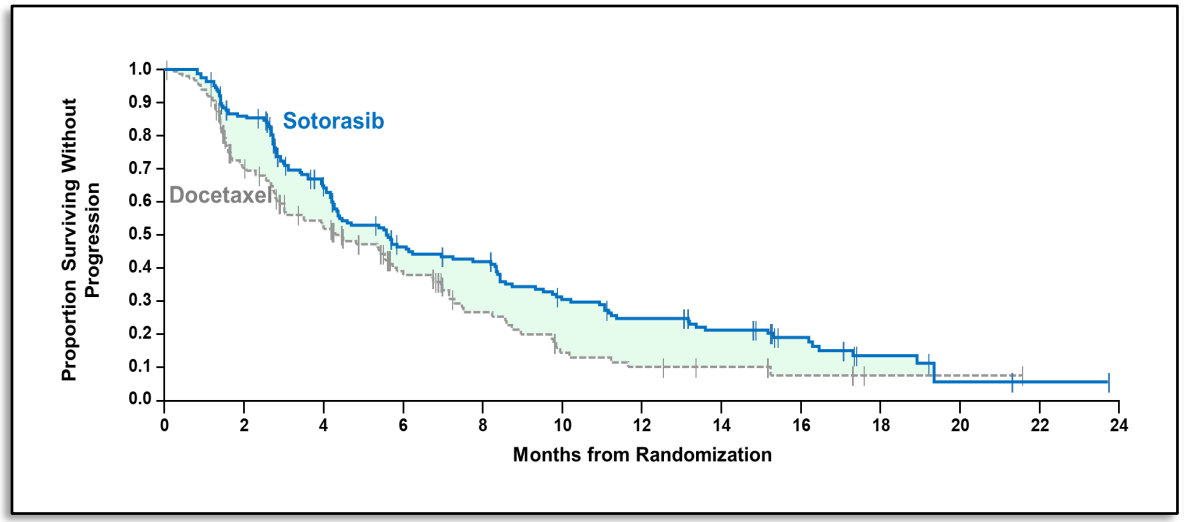


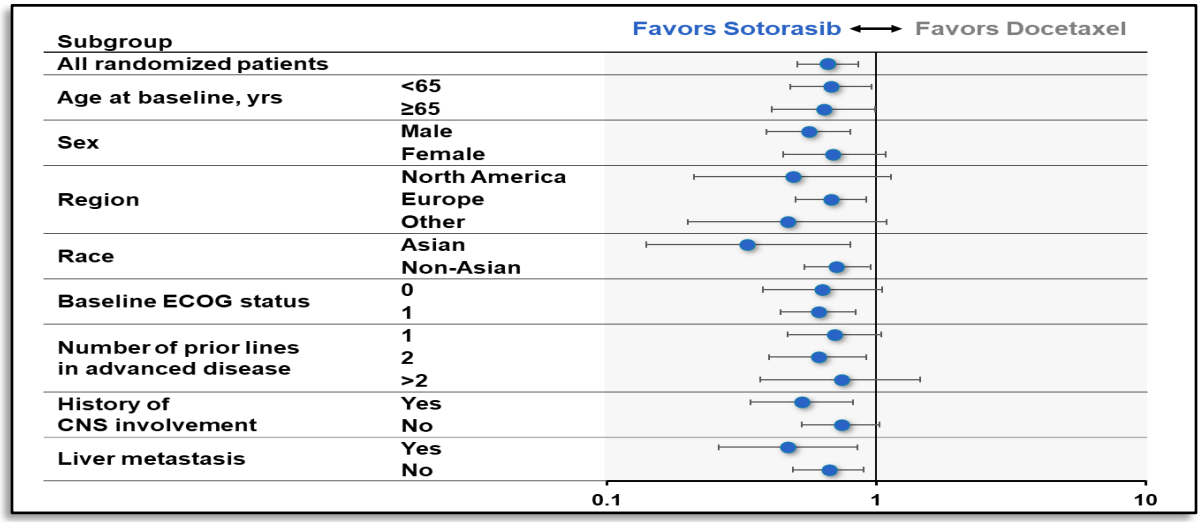
Sotorasib Demonstrated Meaningful Efficacy Benefits Compared to Docetaxel

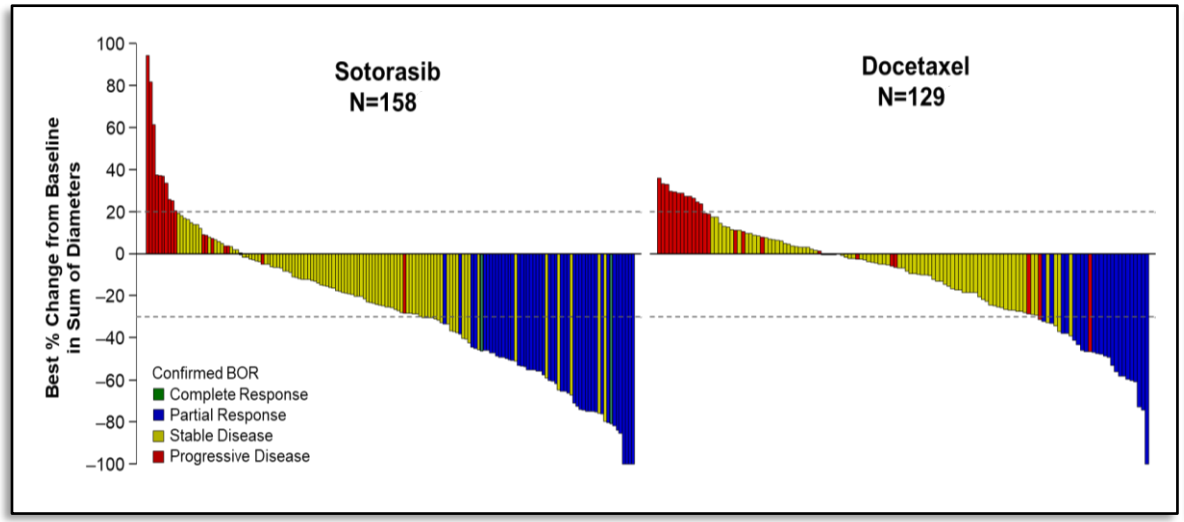
Patient Reported Outcomes

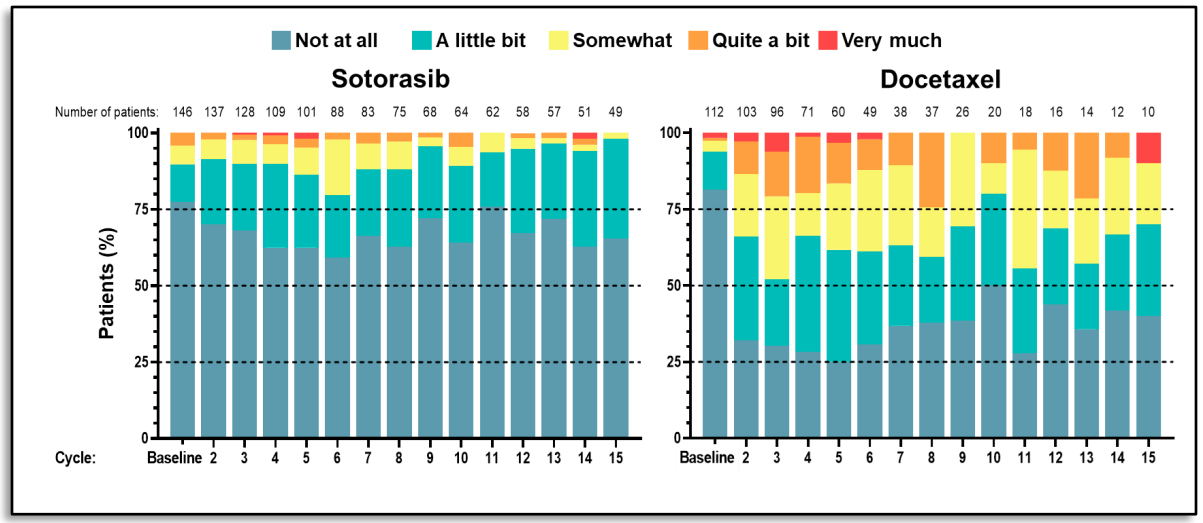


Sotorasib Demonstrated Meaningful Efficacy Benefits Compared to Docetaxel

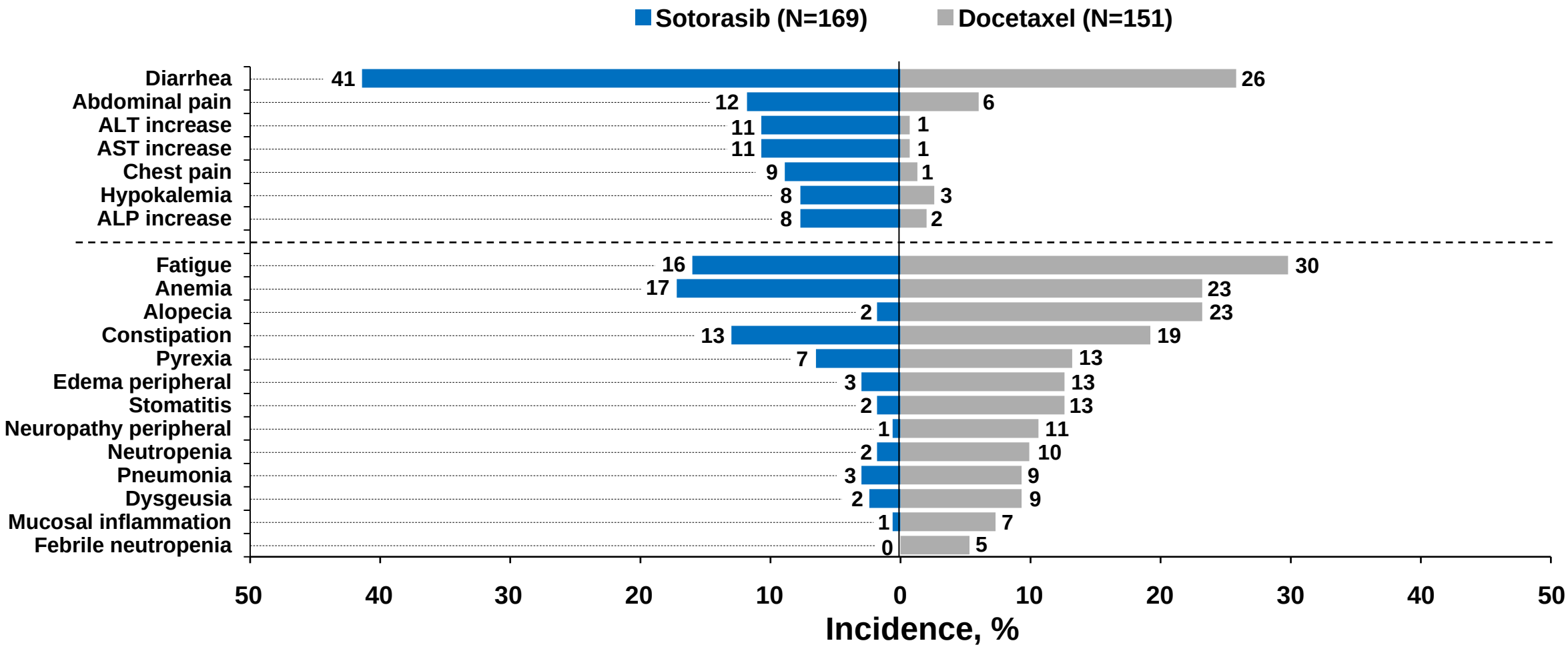








Sotorasib has an Established and Manageable Toxicity Profile



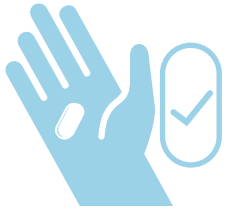
Common AEs with 5% difference in incidence rate

CC-100

My Perspective

Considerations for second-line *KRAS p.G12C*-mutated NSCLC

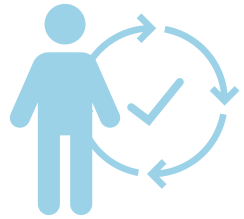
Oral Dosing



Efficacy

Safety

Overall Patient Experience



Sotorasib for the Treatment of Adult Patients with *KRAS p.G12C*-mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Oncologic Drugs Advisory Committee

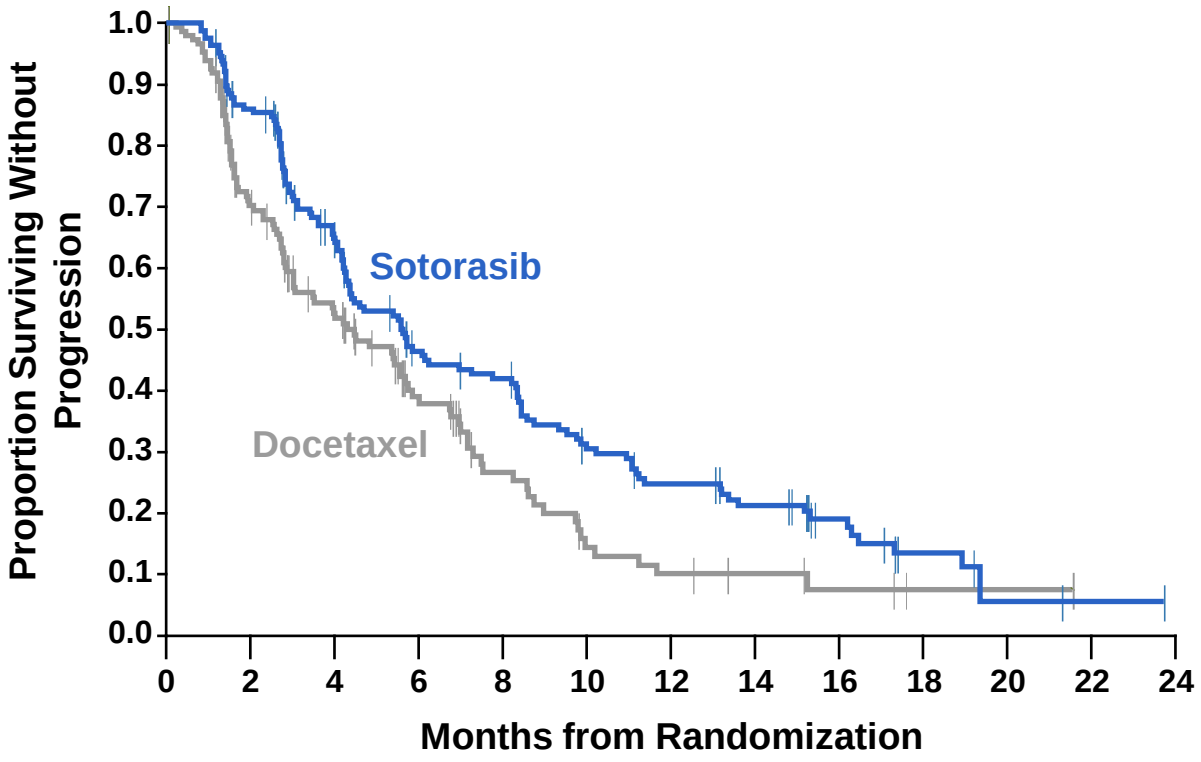
October 5, 2023

AMGEN®

CC-102

Backup Slides Shown During Question and Answer

PFS by Blinded Central Review

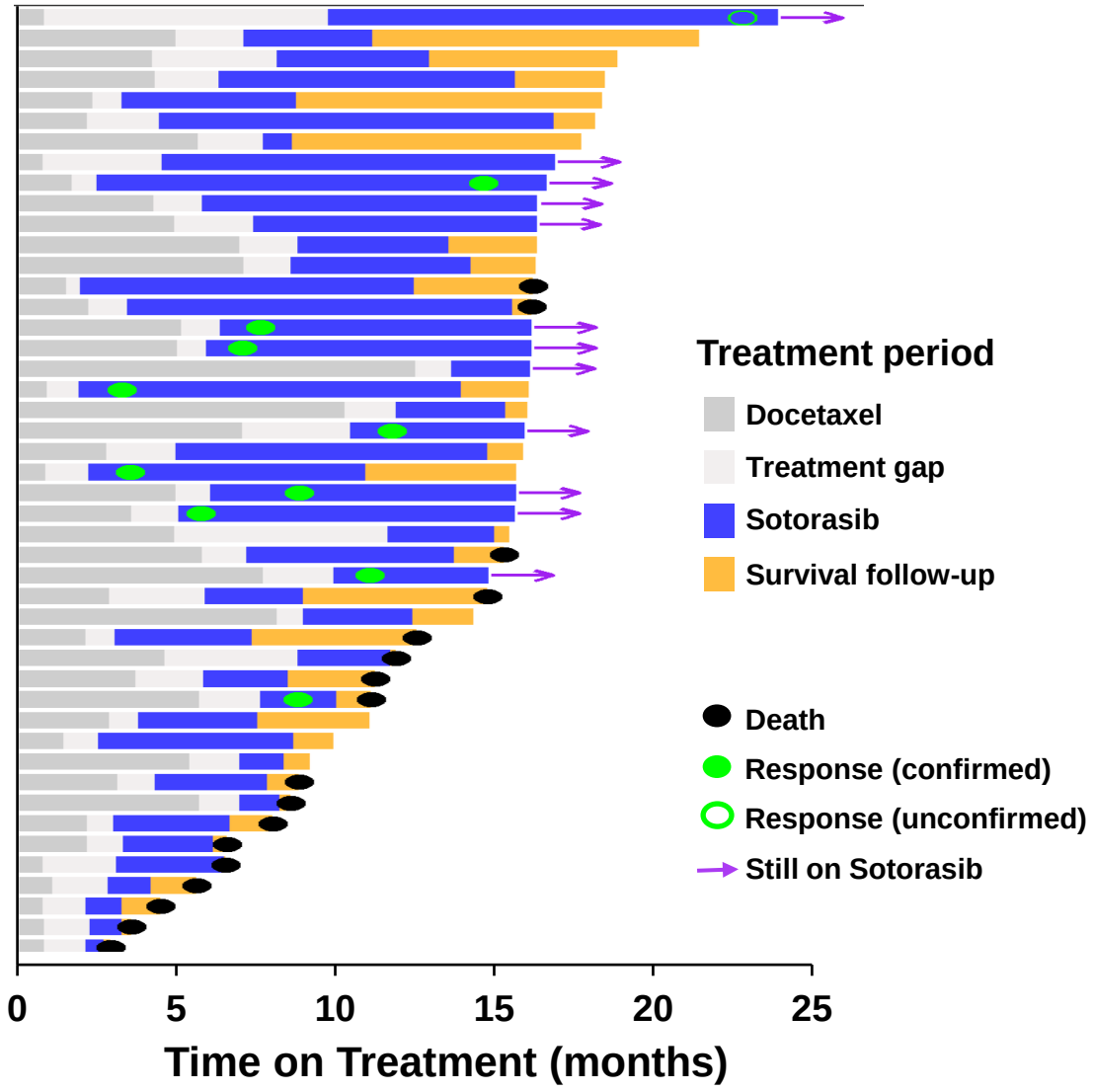


Number of Patients at Risk:

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 N=171	Docetaxel N=174	
Events, n (%)	122 (71.3)	101 (58.0)	
HR (95% CI)	**0.66 (0.51, 0.86)**		
***p*-value (2-sided)**	**0.003**		
Median PFS (95% CI), months	**5.6** (4.3, 7.8)	**4.5** (3.0, 5.7)	
PFS rate (95% CI), %			**Difference**
At 3 months	71.7 (64.0, 78.1)	59.4 (50.7, 67.1)	**12.3%**
At 6 months	46.5 (38.3, 54.3)	39.1 (30.2, 47.8)	**7.4%**
At 9 months	34.4 (26.7, 42.2)	20.2 (12.5, 28.9)	**14.4%**
At 12 months	24.8 (17.9, 32.4)	10.1 (4.7, 18.0)	**14.7%**
At 15 months	21.3 (14.7, 28.7)	10.1 (4.7, 18.0)	**11.2%**
Percentile (95% CI), months			
75th percentile	2.8 (2.7, 3.6)	1.6 (1.5, 2.5)	**1.2** months
60th percentile	4.2 (3.6, 5.4)	2.9 (2.3, 4.0)	**1.3** months
50th percentile	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)	**1.1** months
40th percentile	8.3 (5.7, 9.8)	5.8 (4.5, 7.2)	**2.5** months
25th percentile	11.4 (9.8, 16.3)	8.6 (7.0, 9.9)	**2.8** months

On-Protocol Crossover Subjects



	On-Protocol Crossover Subjects N=46
Number of sites, countries	43 sites, 18 countries
Time on sotorasib (months)	
Median (range)	4.8 (0.6, 14.3)
Still on sotorasib, n (%)	12 (26)
Confirmed ORR post crossover, n (%)	10 (21)
Median DOR (95% CI), months	10.6 (2.1, NE)
ORR with unconfirmed response, n (%)	11 (23.9)
DCR post crossover, n (%)	35 (76.1)
Median OS since randomization (95% CI), months	NE (15.3-NE)

ORR, DOR post crossover is per investigator

PFS Sensitivity Analysis to Address Early Dropout in Docetaxel (Impute with Patients PFS ≥12 Weeks)

Imputation Results (Based on 20000 Simulations)

Imputed Subjects by Resampling	Average HR (95% CI)	Proportion of Times Imputations Showed PFS Superiority of Sotorasib
23 untreated in docetaxel	0.73 (0.57, 0.95)	83.9%

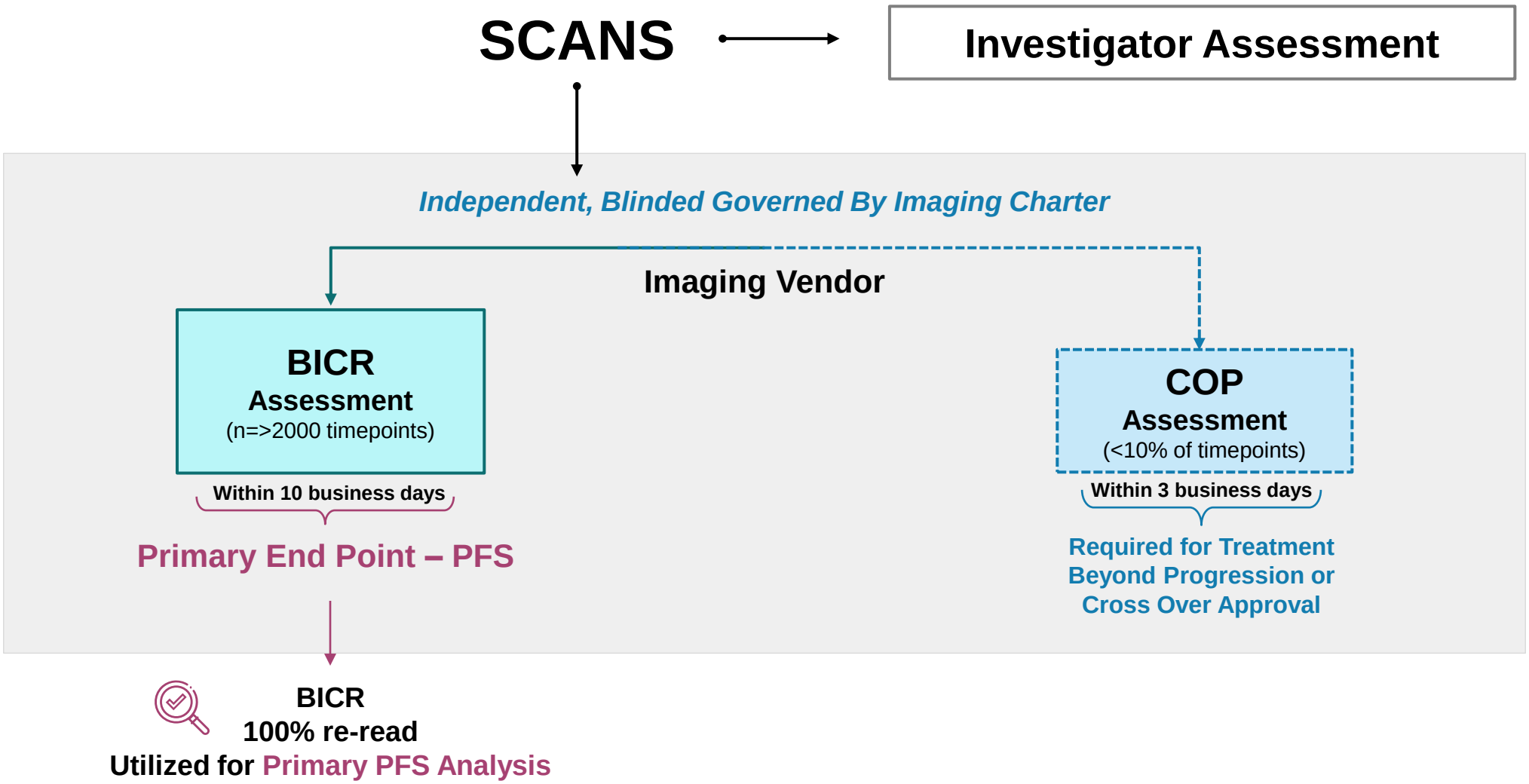
- **For 23 docetaxel untreated and censored subjects, resampling was performed within treatment group and stratum who continued beyond 12 weeks without progression**
- **PFS superiority threshold is p<0.044**

Withdrawal Rates Across Open-Label Studies

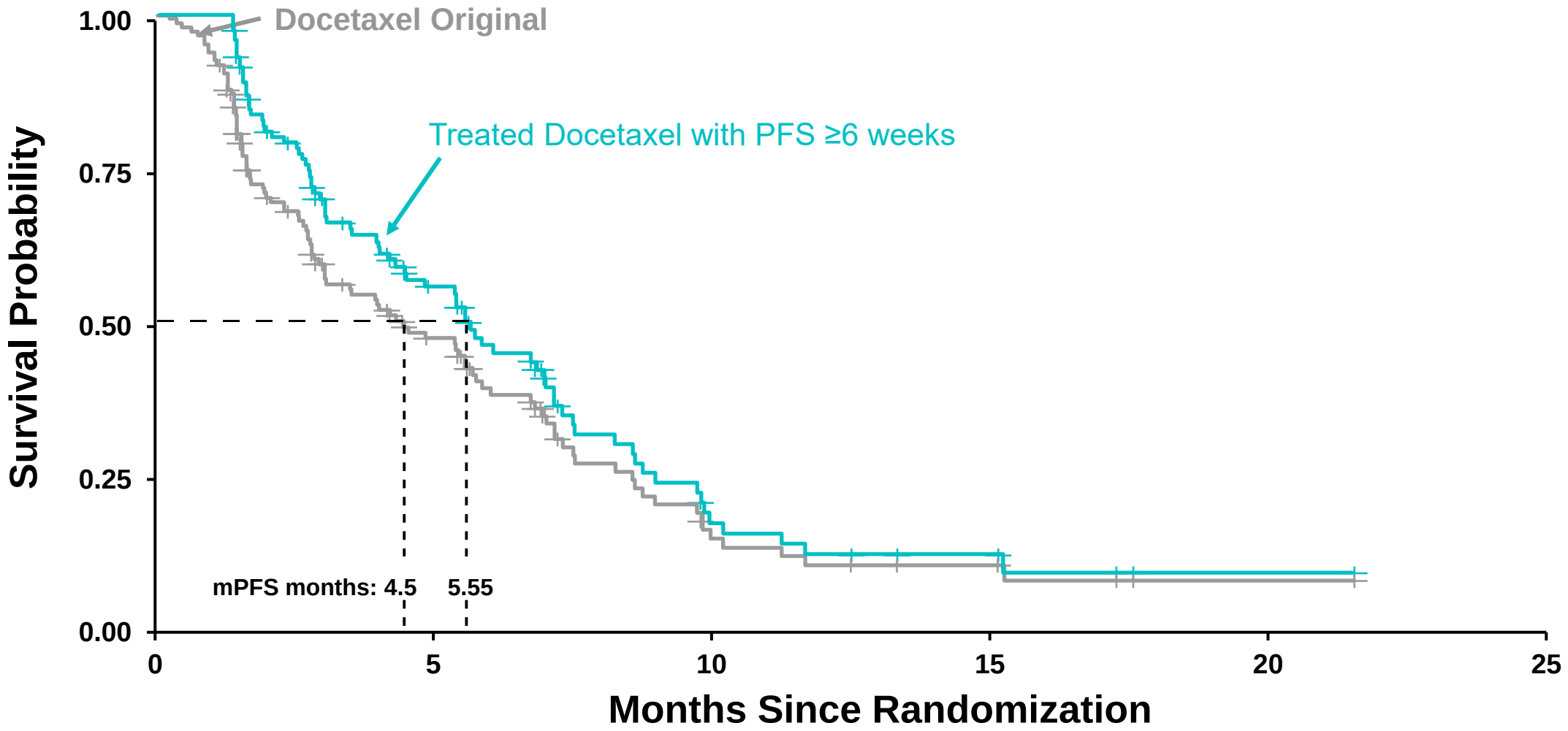
	CB200[a]	KN010[b]	CM057[c]	Javelin Lung 200[d]
Study drug	Sotorasib	Pembrolizumab	Nivolumab	Avelumab
Comparator	Docetaxel	Docetaxel	Docetaxel	Docetaxel
Design	Open	Open	Open	Open
Tumor	NSCLC	NSCLC	NSCLC	NSCLC
Start Date	June 4, 2020	Aug 28, 2013	Nov 2012	March 24, 2015
Withdrawal prior to study drug	**Doce: 13%**	**Doce: 10%**	**Doce: 8%**	**Doce: 8%**
	Soto: 1%	Pembro: 1%	Nivo: 1.7%	Avelu: <1%
Withdrawal after study drug start	**Doce: 7%**	**Doce: 14%**	**Doce: 8%**	**Doce: 7%**
	Soto: 4%	Pembro: 3%	Nivo: 3%	Avelu: 3%

a. de Langen et al, *Lancet* 2023; 401: 733-46.; b. Herbst et al, *Lancet* 2016; 387: 1540-50.; c. Borghaei et al, *N Engl J Med* 2015; 373: 1627-39
d. Barlesi et al, *Lancet Oncol* 2018; 19: 1468-79

Imaging Evaluation Pathway
Confirmation of Progression Procedure in CB200

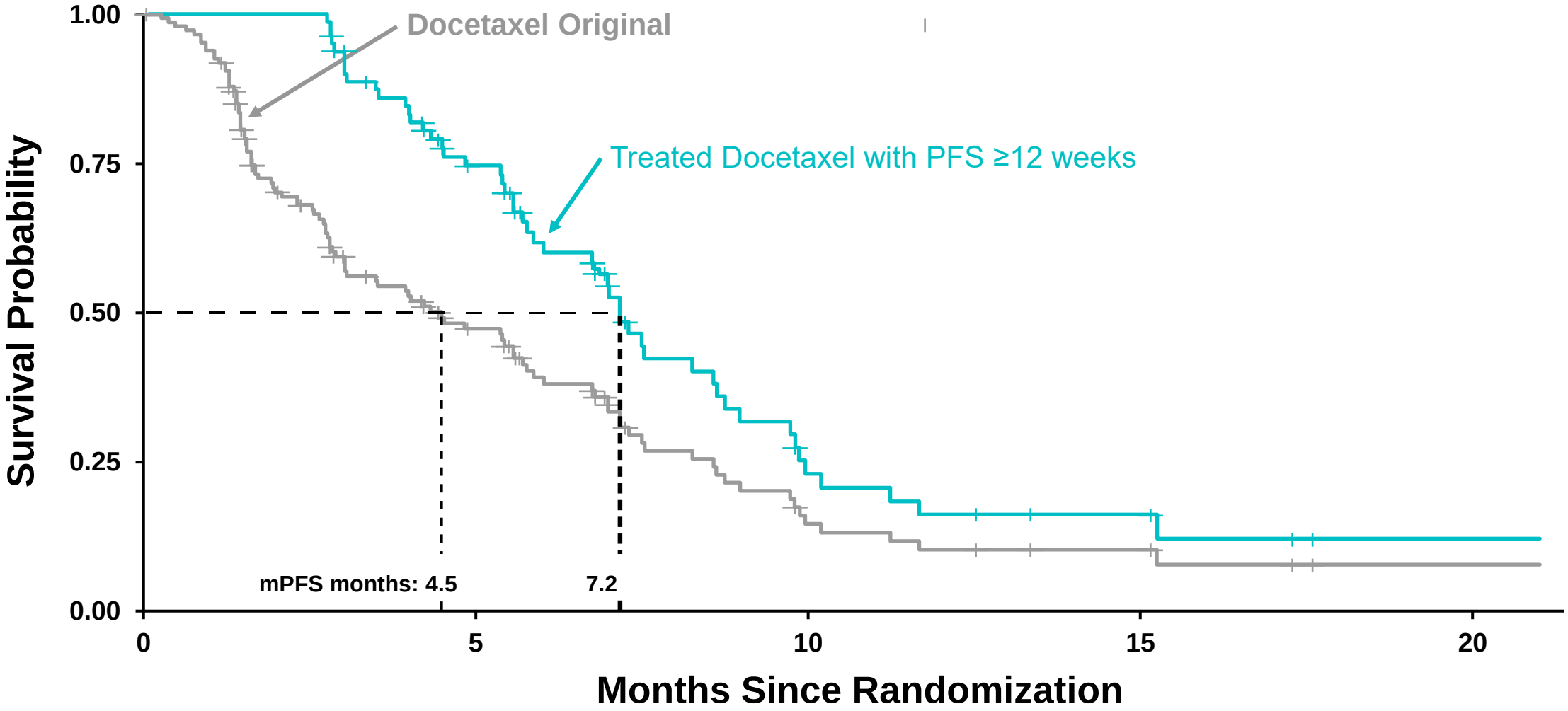


Basis of Amgen Imputation:
Docetaxel Treated Subset With PFS ≥6 Weeks



BU-636

Basis of Amgen Imputation:
Docetaxel Treated Subset With PFS ≥12 Weeks



BU-637

OS Restricted Mean Survival Time (RMST)

CodeBreaK 200 at 90 Day Update

RMST up to	Sotorasib (months)	Docetaxel (months)	Difference (95%CI) (months)	Average RMST Difference/ Duration of Follow-up (95% CI)
22 months	12.33	12.19	0.14 (-1.59, 1.87)	0.6% (-7.2%, 8.5%)
24 months	12.87	12.71	0.17 (-1.71, 2.05)	0.7% (-7.1%, 8.5%)

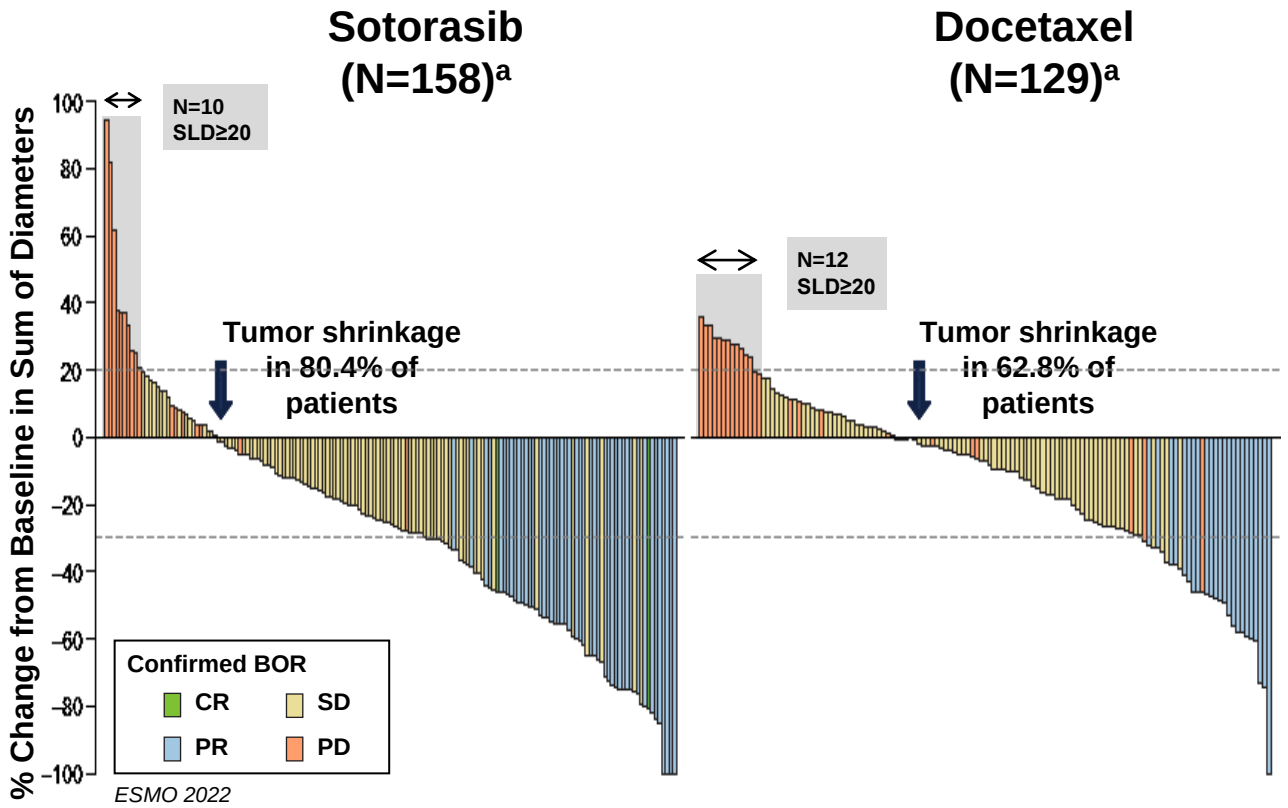
At 22-24 months, 9%-16% patients remained at risk

With 24 months of OS follow up, the average survival time is 0.17m longer and the average OS rate is 0.7% higher for sotorasib compared to docetaxel.

No Significant Enrichment of Co-alterations in Small Set of Subjects with Tumor SLD Change ≥20% in Either the Sotorasib/Docetaxel Arm

Comparison of patients with/without SLD20 ≥20% to assess if a genomic feature is associated with lack of response and tumor growth in the presence of sotorasib/docetaxel

Caveat: small sample size and multiple testing limits interpretation

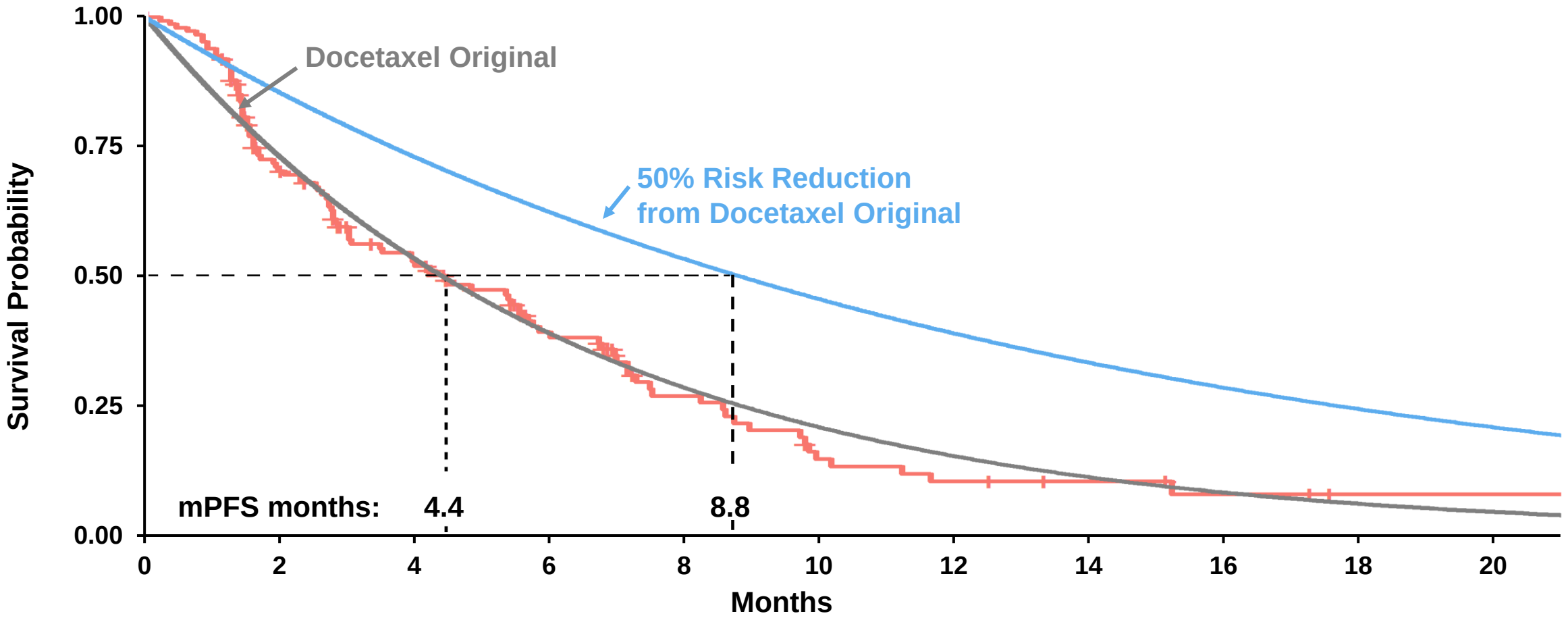


Arm	Number of Subjects: SLD ≥20 (yes)	SLD ≥20 (no)	Biomarker Evaluable SLD ≥20 (yes)	Biomarker Evaluable SLD ≥20 (no)
Sotorasib	10	148	6 (tissue) 8 (plasma)	105 (tissue) 137 (plasma)
Docetaxel	12	117	5 (tissue) 12 (plasma)	79 (tissue) 103 (plasma)

After false discovery rate correction to account for multiple testing
Tempus 648 gene xT panel for tissue, Resolution Bioscience ctDx Lung 23 gene panel for plasma
a. Patients without baseline target lesions or post-baseline percent changes, or with BOR of NE are not shown; † Median of best percent change from baseline in sum of diameters for confirmed responders;

Basis of FDA Tipping Point Analysis

Risk of Event 50% Lower Than Other Patients in Docetaxel



Based on Exponential distribution

BU-697

Target Lesion Percent Changes in Docetaxel Patients Who Crossed-over Early

	% Change in Lesion Size	
Patient	Reader 1	Reader 2
1	-16.5	-1.9
2	-10.5	5.5
3	-10.5	4.5
4	-7.1	2.0
5	-6.3	19.2
6	-3.0	9.9
7	-2.2	2.3
8	-1.1	-5.7
9	-0.1	9.7
10	0.0	-9.7

	% Change in Lesion Size	
Patient	Reader 1	Reader 2
11	1.4	25.1
12	2.2	16.4
13	3.7	6.0
14	4.6	36.1
15	6.9	-2.7
16	9.5	0.6
17	10.2	14.2
18	18.5	21.6
19	missing	