Poziotinib for NSCLC Harboring HER2 Exon 20 Insertion Mutations

Spectrum Pharmaceuticals

Oncologic Drugs Advisory Committee

September 22, 2022

Poziotinib Introduction

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Poziotinib: Oral, Irreversible Tyrosine Kinase Inhibitor (TKI)

- Patients with non-small cell lung cancer (NSCLC) harboring HER2 exon 20 insertion mutations need effective and safe therapy
- In these patients, Poziotinib is
  - Clinically effective
  - Safe
- Currently no approved oral treatment options

FDA Granted Fast Track Designation for Poziotinib in Proposed Indication

For the treatment of patients with previously treated locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring HER2 exon 20 insertion mutations

Overall Clinical Development Program

- Greater than 1,336 patients and 82 healthy volunteers
- 22 studies
  - Extensive dose evaluation conducted in 7 studies
  - Exploration of doses from 0.5 mg – 32 mg QD
  - Continuous vs intermittent dosing
  - 1 positive pivotal study
  - 2 supportive studies
- Expanded access program

Data cutoff: May 16, 2022

Efficacy in NSCLC Patients Harboring HER2 Exon 20 Insertion Mutations Receiving Poziotinib 16 mg QD

	Second Line			First Line
	Pivotal Study	Supportive Data	Supportive Data	Additional Data
	Study 202 Cohort 2	Study 202 Cohort 5	MDACC Study[1]	Study 202 Cohort 4
N	90	10	27	47
ORR	28%	40%	26%	45%

1. Elamin et al., 2022

Poziotinib Meets Criteria for Accelerated Approval

Qualifying Criteria	Poziotinib Fulfills Criteria
Treats serious condition	NSCLC HER2 exon 20 insertion mutation recognized as a rare, life-threatening disease[1]
Provides meaningful advantage over available therapies	ORR of 28% exceeding available therapies
Surrogate endpoint likely to predict clinical benefit	Demonstrated evidence of efficacy with protocol defined endpoint of ORR, an intermediate clinical endpoint that is reasonably likely to predict clinical long-term benefit (improved survival)
Post-approval trial required to confirm benefit	Confirmatory study, Study 301, currently underway to confirm clinical benefit in patients with NSCLC harboring HER2 exon 20 insertion mutations

1. Wu et al., 2021

Key Points for Discussion

	Sponsor Position
Efficacy	• Unmet need for HER2 Exon 20 NSCLC remains • Poziotinib ORR of 28% is higher than available agents in second line for NSCLC • Met primary efficacy endpoint
Safety	• High rates of Grade 3/4 diarrhea, rash; low permanent discontinuation • Oncologists are medically experienced in handling TKI AEs • Low 0.8% fatal pneumonitis
Dose optimization	• Extensively studied • 7 studies with 404 patients ranging from 0.5 to 32 mg daily • 16 mg QD met primary endpoint, tolerated with allowed dose modification
Confirmatory trial	• Confirmatory study underway at 8 mg BID as agreed with FDA • Sponsor willing to consider protocol amendment • Futility analysis within 2 years

Agenda

Unmet Need and MOA

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Efficacy

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Safety

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Clinical Perspective

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MD Anderson Cancer Center

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Unmet Need and Mechanism of Action

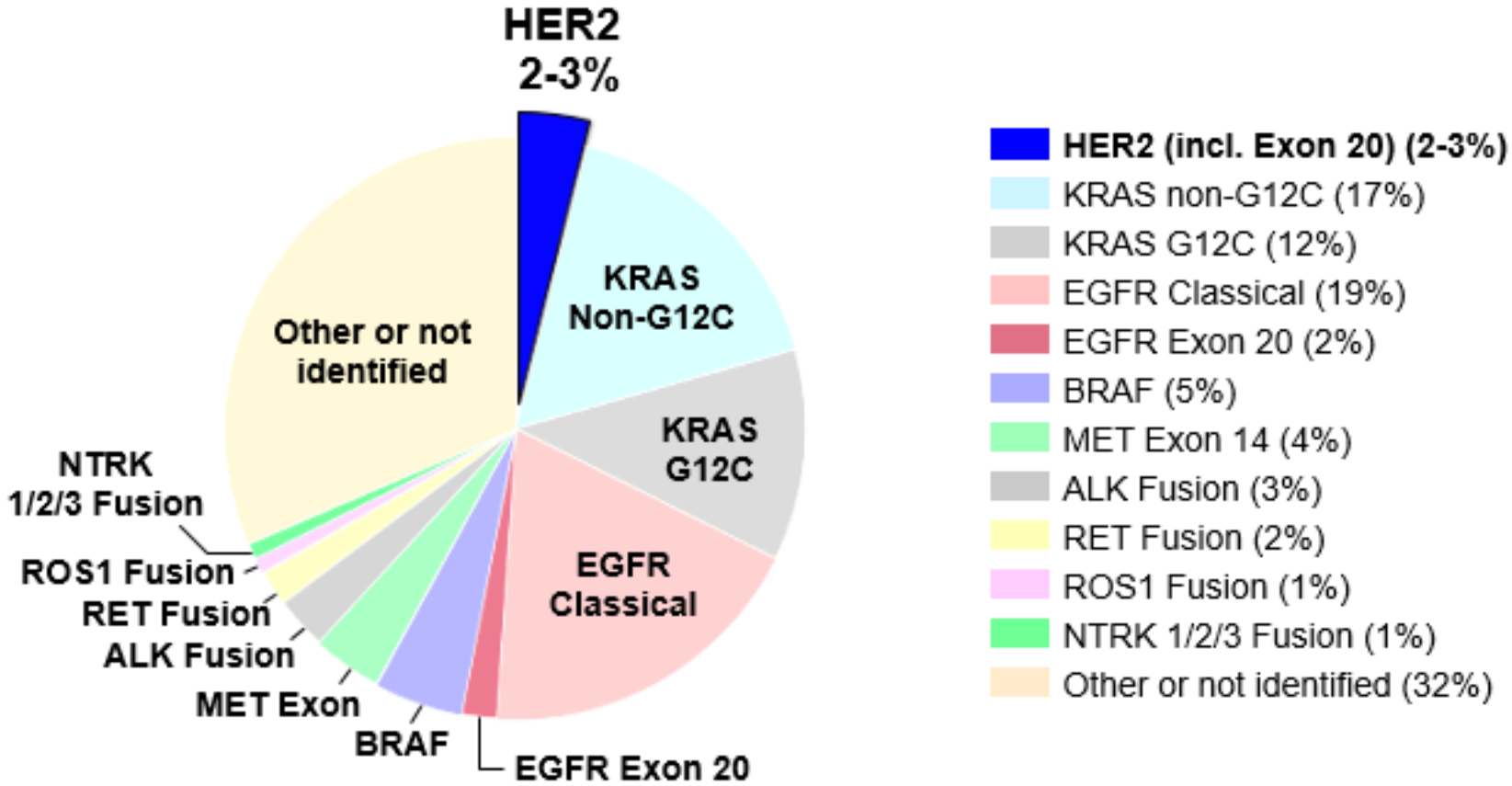
John Heymach, MD, PhD

Professor of Medicine and Chair

Thoracic / Head and Neck Medical Oncology

The University of Texas MD Anderson Cancer Center

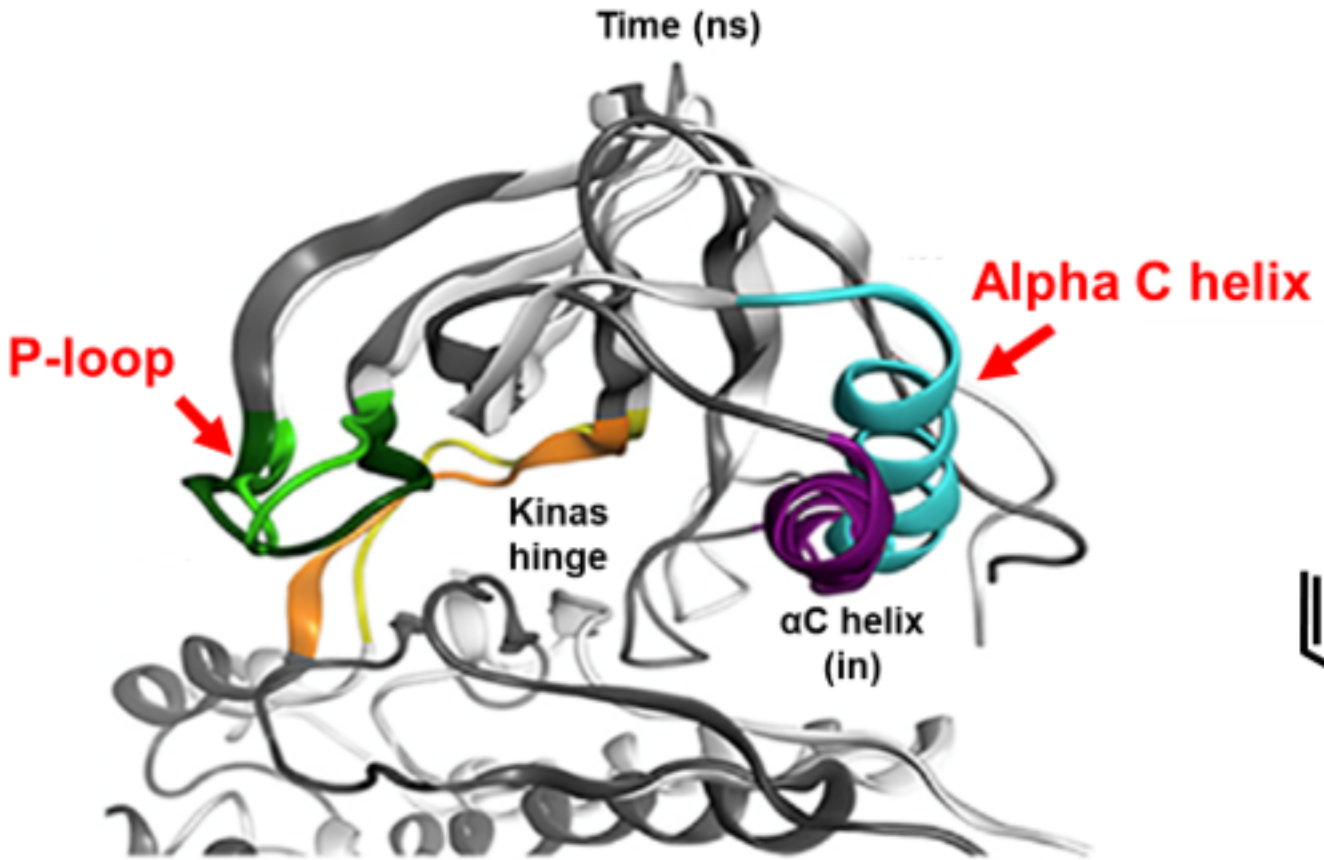
HER2 Exon 20 Insertions Are Targetable Oncogenic Drivers and Therapeutic Targets in NSCLC

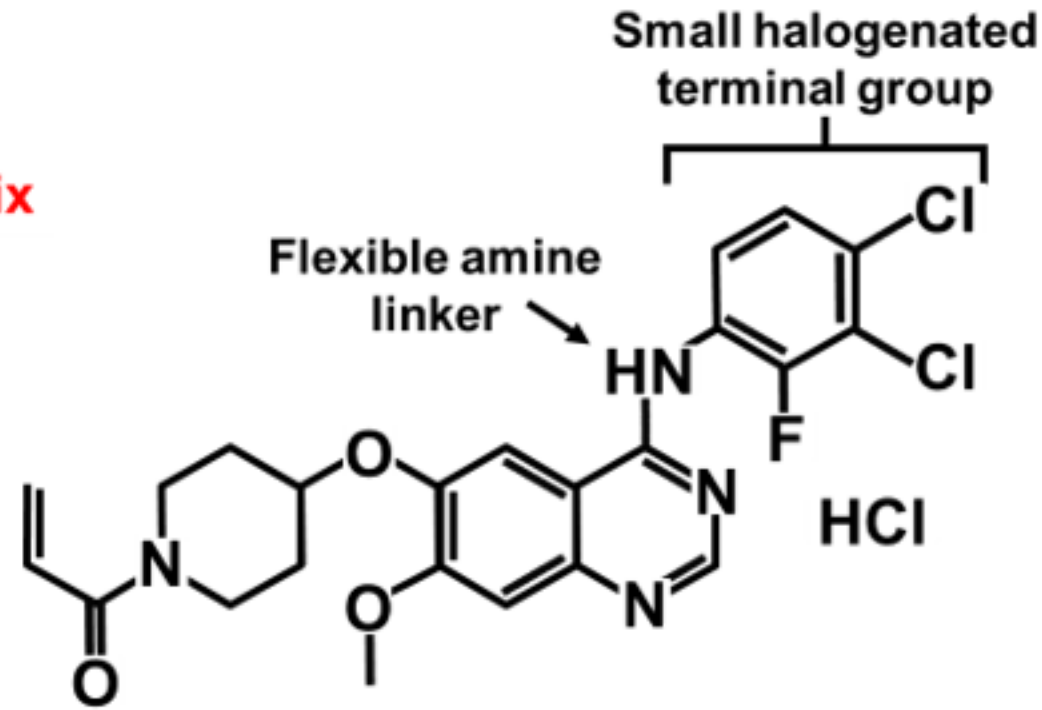


- Majority of HER2 mutations (up to 86%) are Exon 20 insertions

Trinity, US Epi of NSCLC mutations

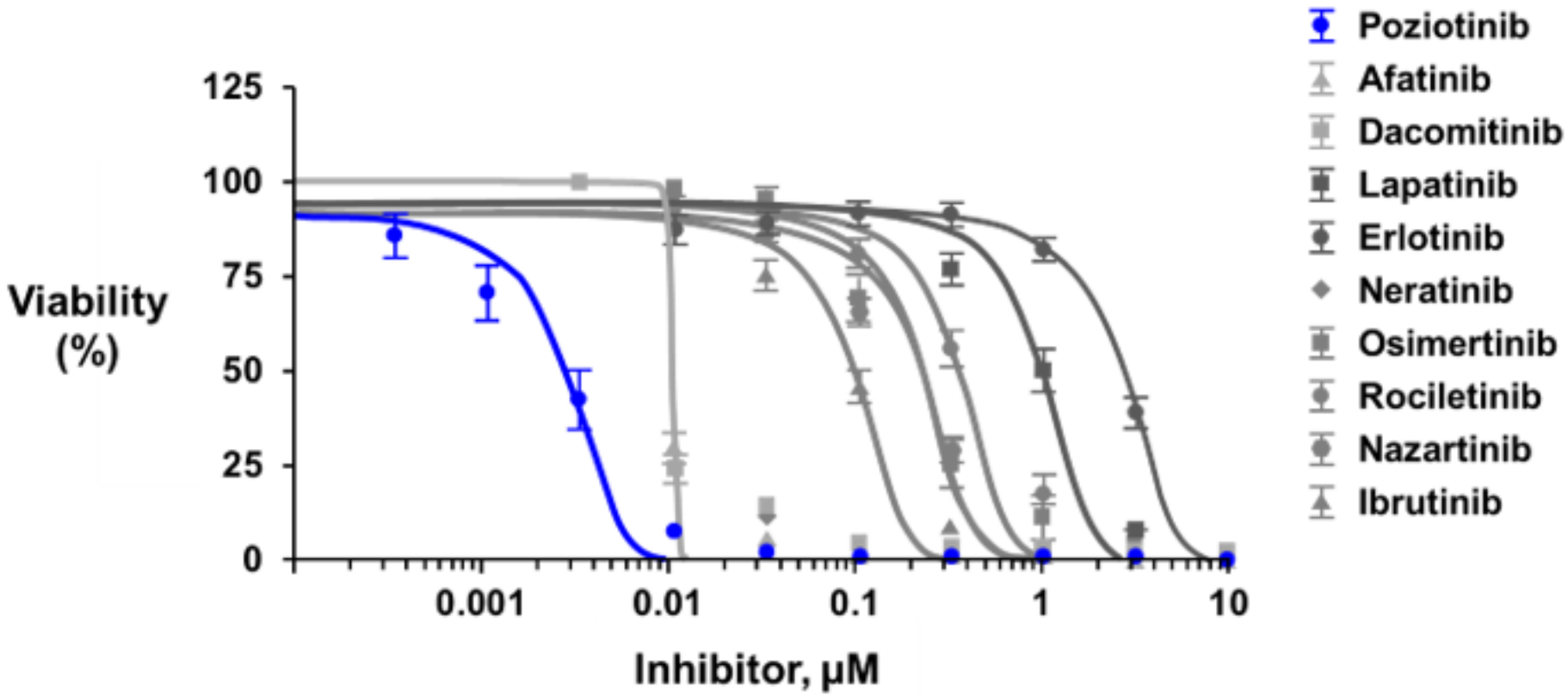
Unique Poziotinib Structure Overcomes Steric Hinderance Induced by HER2 Exon 20 Insertions





Robichaux et al., Cancer Cell 2019

Challenges in Inhibiting HER2 Exon 20 Insertions



Robichaux et al., AACR 2017

Available TKIs Demonstrate Minimal Efficacy in Target Population

Drug	Population	N	ORR (%)	PFS (months)
Neratinib[1]	HER2 Exon 20 ins	17	0	2.9
Neratinib[2]	HER2 Exon 20 ins	26	3.8	5.5
Afatinib[3]	HER2 Exon 20 ins	13	7.7	3.9
Dacomitinib[4]	HER2 Exon 20 ins	26	12	3.0
Afatinib[5]	HER2 mutation	18	0	2.8
Afatinib[6]	HER2 mutation	27	13%	NR

1. clinicaltrials.gov, NCT01827267; 2. SUMMIT study, Hyman et al., *Nature* 2018 (US); 3. NICHE study (Europe), Dziadziuszko et al., *J Thorac Oncol* 2019;
4. Kris et al, 2015 (US); 5. Fan et al., *Lung Cancer* 2020 (China); 6. Lai et al., *Eur J Cancer* 2019 (North America, Australia, Euro)

Limited Efficacy of Chemotherapy for 2L NSCLC

Drug	Study	N	ORR (%)	PFS (months)
Single agent chemotherapy				
Docetaxel used as comparator for RP3 studies	TAX197; TAX320[1]	104; 248	6%	2 – 3[2]
Pemetrexed (if not used 1L)	JMEI[1]	571	9%	2.9
Combination chemotherapy				
Docetaxel plus ramucirumab	REVEL[1]	628	23%	4.5

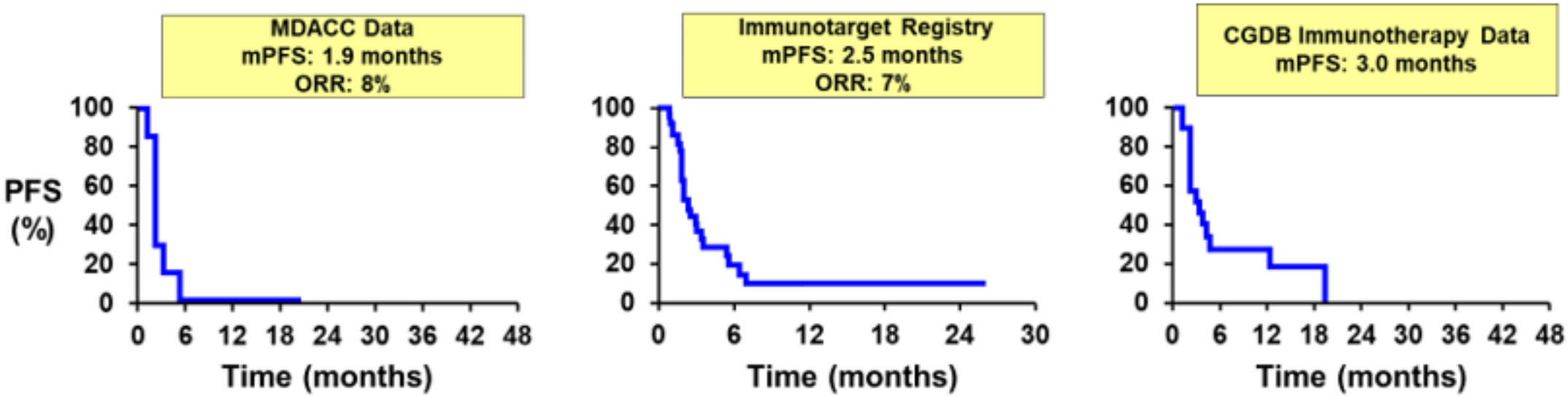
Trastuzumab deruxtecan – not considered available therapy from a regulatory standpoint as it is approved under provisions of accelerated approval (Table 1, page 12, FDA briefing document)

Docetaxel is the most commonly used treatment for 2L HER2 NSCLC and used as standard comparator in randomized controlled trials for 2L NSCLC

1. Package inserts; 2. Time-to-Progression
Adapted from FDA briefing document Table 1

CPIs+Platinum Doublets are Standard 1L Treatment and CPIs are Not Effective as 2L Monotherapy for HER2m NSCLC

- 1L standard: doublet chemotherapy plus CPI (pembrolizumab, atezolizumab / bevacizumab, or ipilimumab / nivolumab)
- Like EGFR or ALK mutant tumors, HER2m NSCLC typically has low PD-L1 and TMB and is poorly responsive to CPI
- As 2L monotherapy, mPFS ranged from 1.9 - 3 months and ORR 7-8% in three large independent datasets



Negrao MV et al., 2021; Mazeires et al., 2019

CPIs for 2L NSCLC: Limited Efficacy in HER2 Mutant Subgroup

Treatment	ORR (%)	mPFS (months)
Overall platinum refractory NSCLC[1]		
Nivolumab (Squamous NSCLC)[2]	20%	3.5 months
Nivolumab (Non-Squamous NSCLC)[2]	19%	2.3 months
Pembrolizumab[2]	19%	4.0 months
Atezolizumab[2]	14%	2.8 months
HER2 mutant NSCLC, PD-(L)1		
MDACC[3]	8%	1.9 months
CPI monotherapy[4]	7%	2.5 months
CGDB Immunotherapy[3]	-	3.0 months

1. FDA Briefing Document Table 1; 2. Package inserts; 3. Negrao MV et al., 2021; 4. Mazeires et al., 2019

Distinct Mechanisms of HER2 TKI and ADC Offer Treatment Options

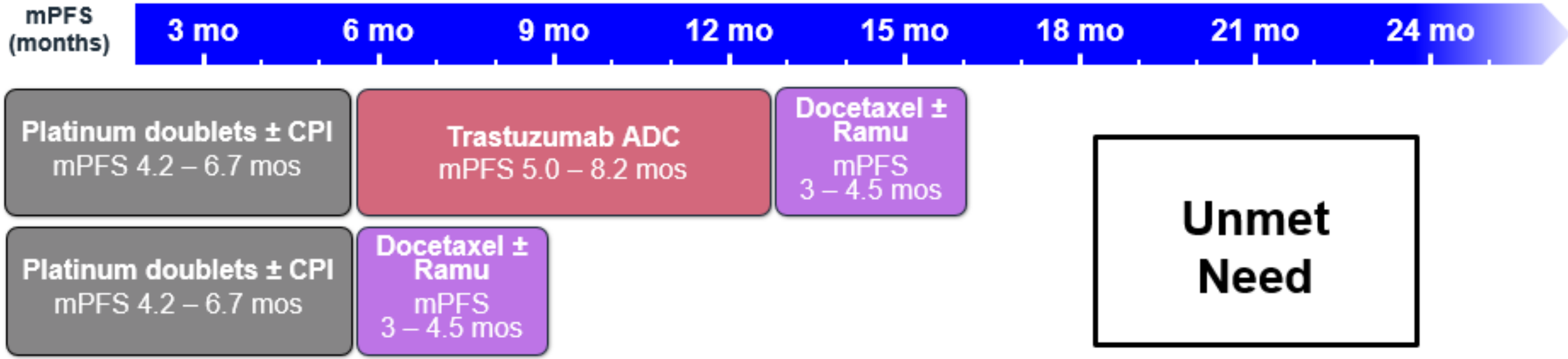
	HER2 TKIs	HER2 ADCs
Route of Administration	**Oral daily**	**IV every 3 weeks**
Mechanism of Action	**Inhibition of kinase signaling**	**Targeted delivery of chemo payload**
Toxicities	**Mechanism related to WT EGFR inhibition (dermatologic, diarrhea)**	**ILD / pneumonitis*, chemo-related, neutropenia**
Mechanisms of Resistance	**Likely TKD mutations, bypass signaling**	**Chemo payload resistance[1-3], downregulation of cell surface target[4]**

Trastuzumab deruxtecan – not considered available therapy from a regulatory standpoint as it is approved under provisions of accelerated approval (Table 1, page 12, FDA briefing document)

*Population limited in clinical study for pulmonary risk

1. Kinneer, 2018; 2. Loganzo et al, 2015; 3. Aldonza et al, 2016; 4. Sung et al., 2018
FDA package insert https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761139s021lbl.pdf; Ricci et al., 2021

Unmet Need for HER2 Exon 20 Insertion NSCLC



- There is an urgent unmet need for effective therapies after platinum doublets (and HER2 ADC if patient is suitable)
- Based on available 2L options, **ORR > 15% or PFS > 4 months** is clearly clinically meaningful for this population
- Patients need an effective oral, targeted treatment with a favorable benefit-risk profile

Efficacy

Gajanan Bhat, PhD

Senior Vice President, Clinical and Data Science

Spectrum Pharmaceuticals, Inc.

Primary and Supportive Evidence of Poziotinib Efficacy in HER2 Exon 20 Insertion Mutation NSCLC

Primary Efficacy

Study 202 Cohort 2 (N = 90)

Previously treated patients with NSCLC harboring HER2 exon 20 insertion mutations

Poziotinib 16 mg QD

Supportive Efficacy

Study 202 Cohort 5 2L HER2 (N = 95)

Randomized Dose-Ranging Study

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Poziotinib 16 mg QD, 8 mg BID, 12 mg QD, 6 mg BID, and 10 mg QD

MDACC Study 2L HER2 (N = 27)

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Poziotinib 16 mg QD

Cohort 2: Study Design

- Eligibility
  - NSCLC harboring HER2 exon 20 insertion mutations
  - Previously treated for locally advanced or metastatic NSCLC with ≥ 1 systemic therapy
  - ≥ 1 target lesion per local investigator using RECIST v1.1
- Poziotinib treatment
  - 16 mg QD for up to 24 months
  - Dose reduced in 2 mg increments in presence of toxicity

Cohort 2: Efficacy Endpoints

- Primary endpoint
  - Objective response rate (ORR) (ie, CR + PR)
    - Independent imaging review committee
    - ORR of 30% with 17% lower bound for 95% CI considered clinically meaningful efficacy based on the efficacy of available therapy and per FDA discussion
    - Analyzed based on As-Treated Population
- Secondary endpoints
  - Disease control rate (DCR) and duration of response (DoR)
  - Progression-free survival (PFS)

Cohort 2: Patient Disposition

Patients Enrolled / Treated
(N = 90)

Discontinued	**89** (99%)
Disease Progression	58%
Adverse Event	16%
Death	11%
Withdrew Consent	6%
Delay of dose for > 28 days since last dose	2%
Lost to follow-up	2%
Initiation of non-protocol therapy	1%
Other	2%

Ongoing
(n = 1)

Cohort 2: Demographics and Baseline Characteristics Representative of Literature

		Poziotinib (N = 90)
Age, years	Mean (SD)	60 (11.69)
	< 65, %	62%
Gender, %	Female	64%
Ethnicity, %	Hispanic or Latino	6%
Race, %	White	78%
	Black	4%
	Asian	13%
	Other	4%
Smoking, %	Never	66%
ECOG, %	Performance status 1	58%

NDA data cutoff

Cohort 2: Heavily Pre-Treated Patients with Systemic Therapy

		Poziotinib (N = 90)
Number of lines of prior systemic therapy	**Median**	**2.0**
	Min, Max	1, 6
	1	**30%**
	2	**31%**
	3+	**39%**
Type of prior systemic therapy	**Chemotherapy**	**98%**
	Platinum-based chemotherapy	**97%**
	Immune checkpoint inhibitor (CPI)	**68%**
	HER2-targeted therapy	**28%**
	VEGF-targeted therapy	**16%**
	TKI-EGFR	**13%**

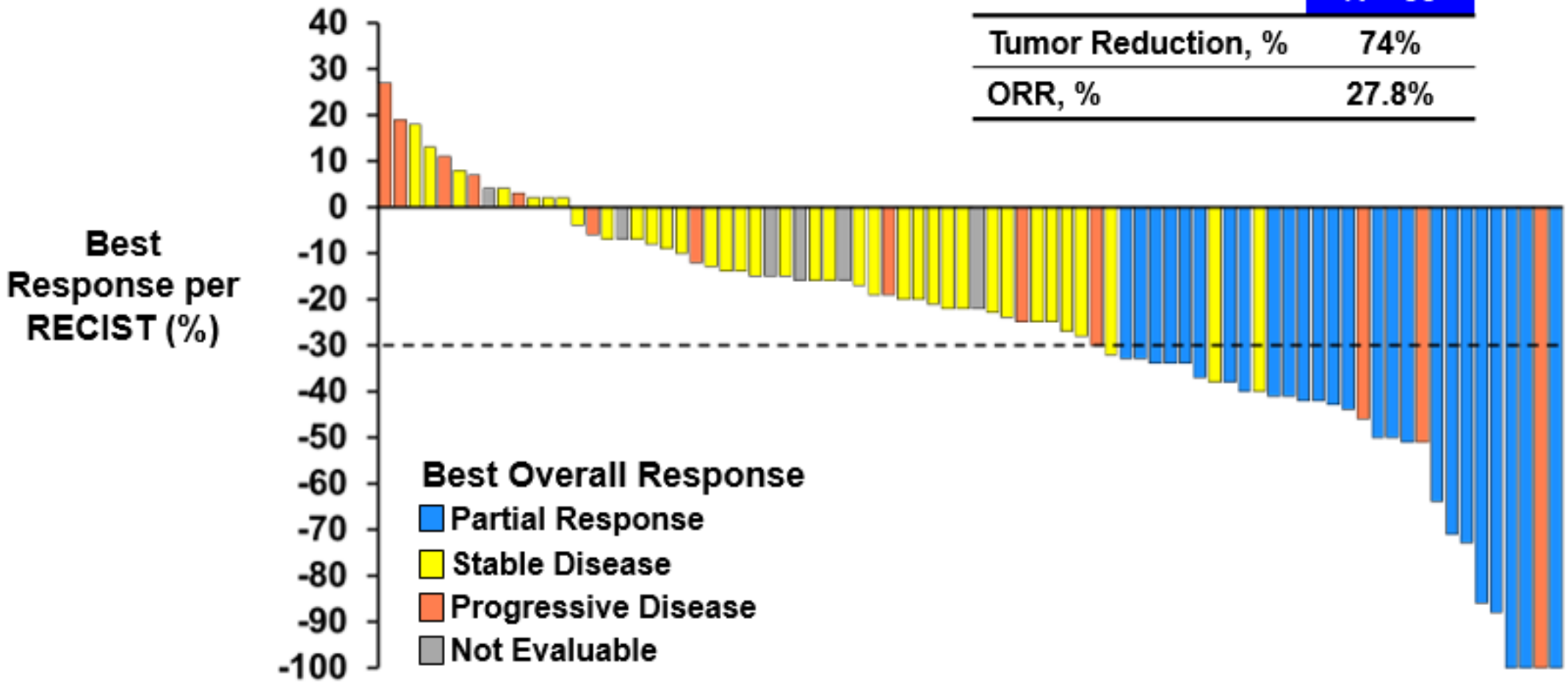
NDA data cutoff

Cohort 2: Met Primary Endpoint Demonstrating Clinically Meaningful Efficacy Over Available Therapies

	As-Treated Population (N = 90)
ORR (CR+PR), %	**27.8%**
95% CI	18.9, 38.2
DCR (CR+PR+SD), %	**70.0%**
95% CI	59.4, 79.2
Confirmed Best Overall Response, %	
Complete response (CR)	**0**
Partial response (PR)	**27.8%**
Stable disease (SD)	**42.2%**
Progressive disease (PD)	**14.4%**
Not evaluable (NE)	**15.6%**

Cohort 2: Tumor Reduction in Majority of Patients

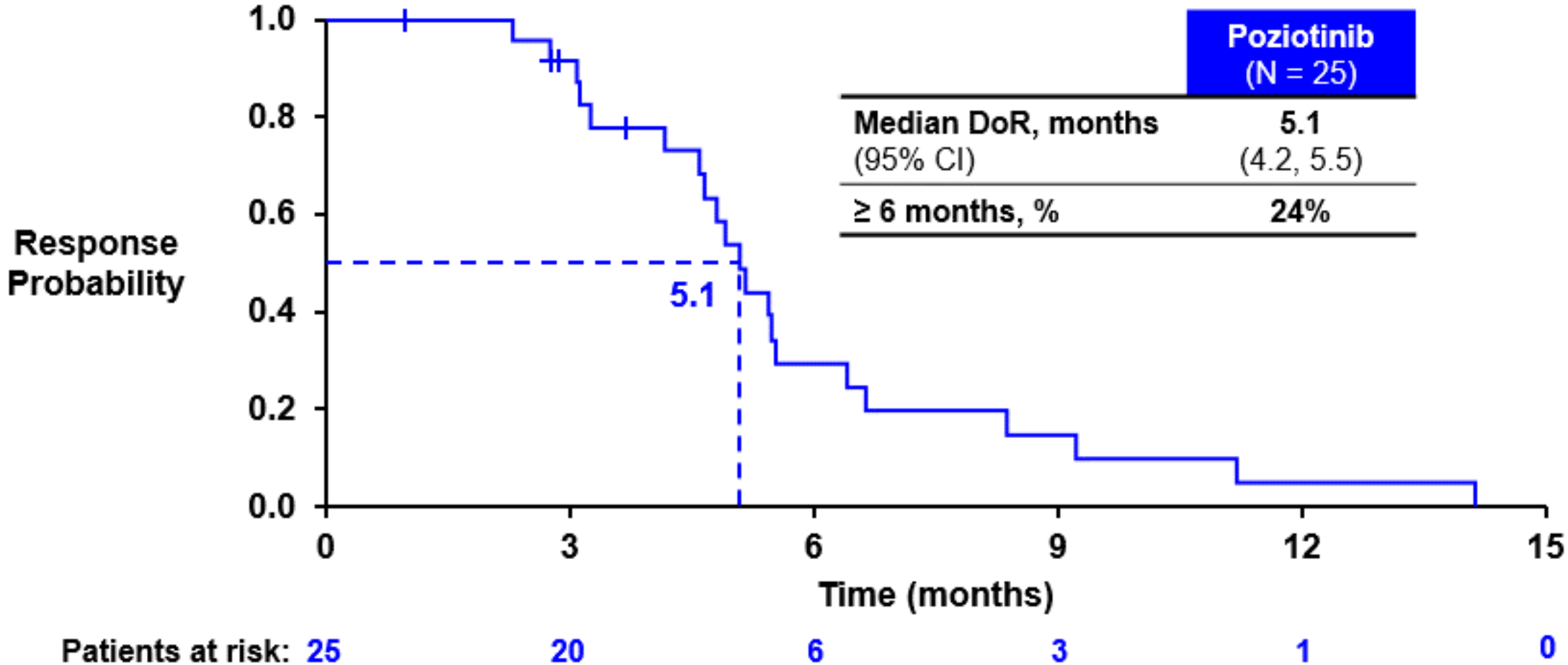
	N = 90
Tumor Reduction, %	74%
ORR, %	27.8%



As-Treated Population

NDA data cutoff

Cohort 2: Durable Responses with Poziotinib

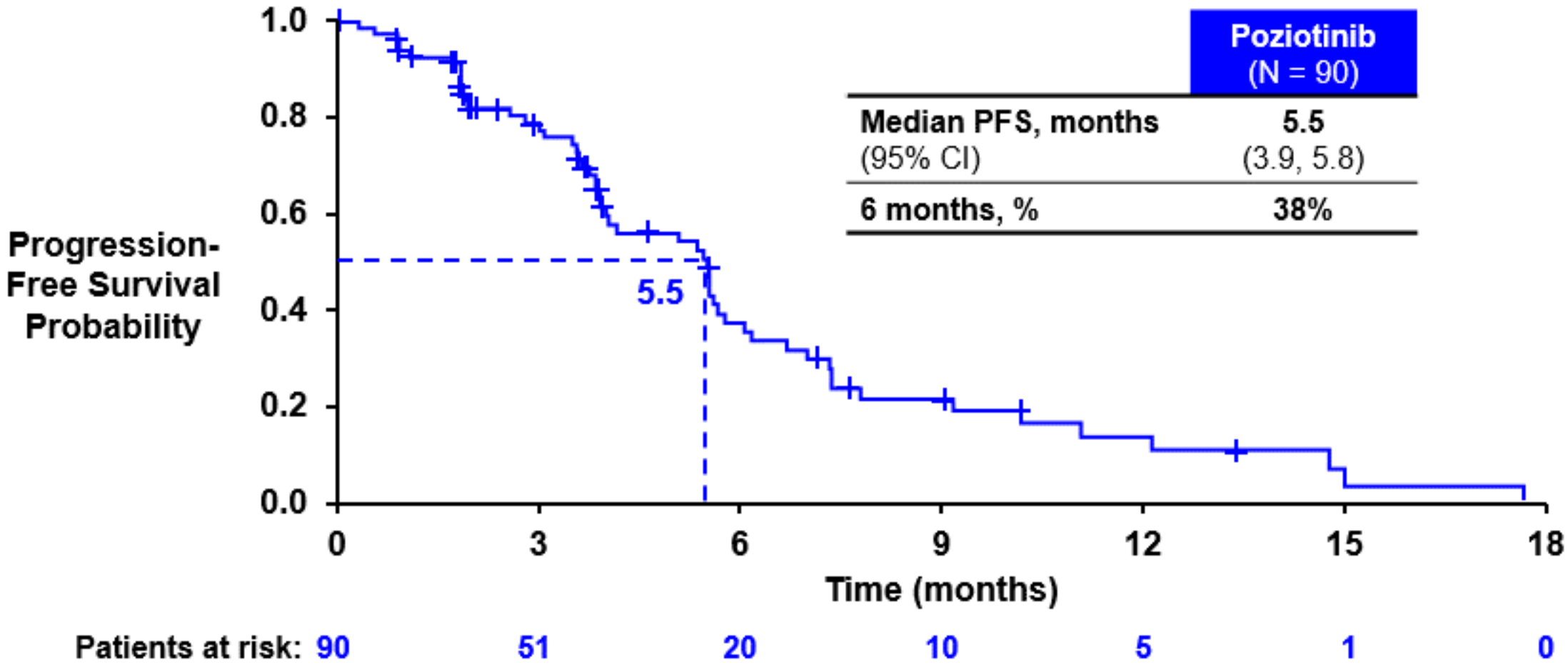


	Poziotinib (N = 25)
Median DoR, months (95% CI)	5.1 (4.2, 5.5)
≥ 6 months, %	24%

As-Treated Population

NDA data cutoff

Cohort 2: Progression-Free Survival



	Poziotinib (N = 90)
Median PFS, months (95% CI)	5.5 (3.9, 5.8)
6 months, %	38%

As-Treated Population

NDA data cutoff

Cohort 2: Consistent Efficacy Across Subgroups

	N	ORR, % (95% CI)
All patients	90	**27.8%** (19, 38)
< 65 years	56	**25.0%** (14, 38)
≥ 65 years	34	**32.4%** (17, 51)
Female	58	**25.9%** (15, 39)
Male	32	**31.3%** (16, 50)
ECOG = 0	38	**31.6%** (18, 49)
ECOG = 1	52	**25.0%** (14, 39)
With brain lesions	14	**28.6%** (8, 58)
1 Line	27	**22.2%** (9, 42)
2 Lines	28	**21.4%** (8, 41)
3+ Lines	35	**37.1%** (22, 55)

As-Treated Population

NDA data cutoff

Cohort 2: Efficacy by Lines of Therapy

Number of Prior Lines of Systemic Therapy	n / N	ORR, % (95% CI)	DCR, %	mDOR (mos)	mPFS (mos)
1 Line	6 / 27	**22.2%** (8.6, 42.3)	66.7%	3.9	5.4
2 Lines	6 / 28	**21.4%** (8.3, 41.0)	67.9%	6.9	6.2
3+ Lines	13 / 35	**37.1%** (21.5, 55.1)	74.3%	5.2	5.5

Cohort 2: Efficacy by Types of Prior Therapy

Type of Prior Systemic Therapy	ORR, % n / N	ORR, % (95% CI)	DCR, %	mDOR (mos)	mPFS (mos)
Platinum-based Chemotherapy	24 / 87	**27.6%** (18.5, 38.2)	**70.1%**	**5.1**	**5.5**
Immune Checkpoint Inhibitor	16 / 61	**26.2%** (15.8, 39.1)	**68.9%**	**5.1**	**5.5**
Tyrosine Kinase Inhibitors (TKI)	6 / 12	**50.0%** (21.1, 78.9)	**91.7%**	**5.2**	**7.0**
HER2 Targeted Therapy	6 / 25	**24.0%** (9.4, 45.1)	**68.0%**	**5.2**	**5.6**
Platinum-based Chemotherapy, Immune Checkpoint Inhibitor	15 / 59	**25.4%** (15.0, 38.4)	**69.5%**	**5.1**	**5.5**

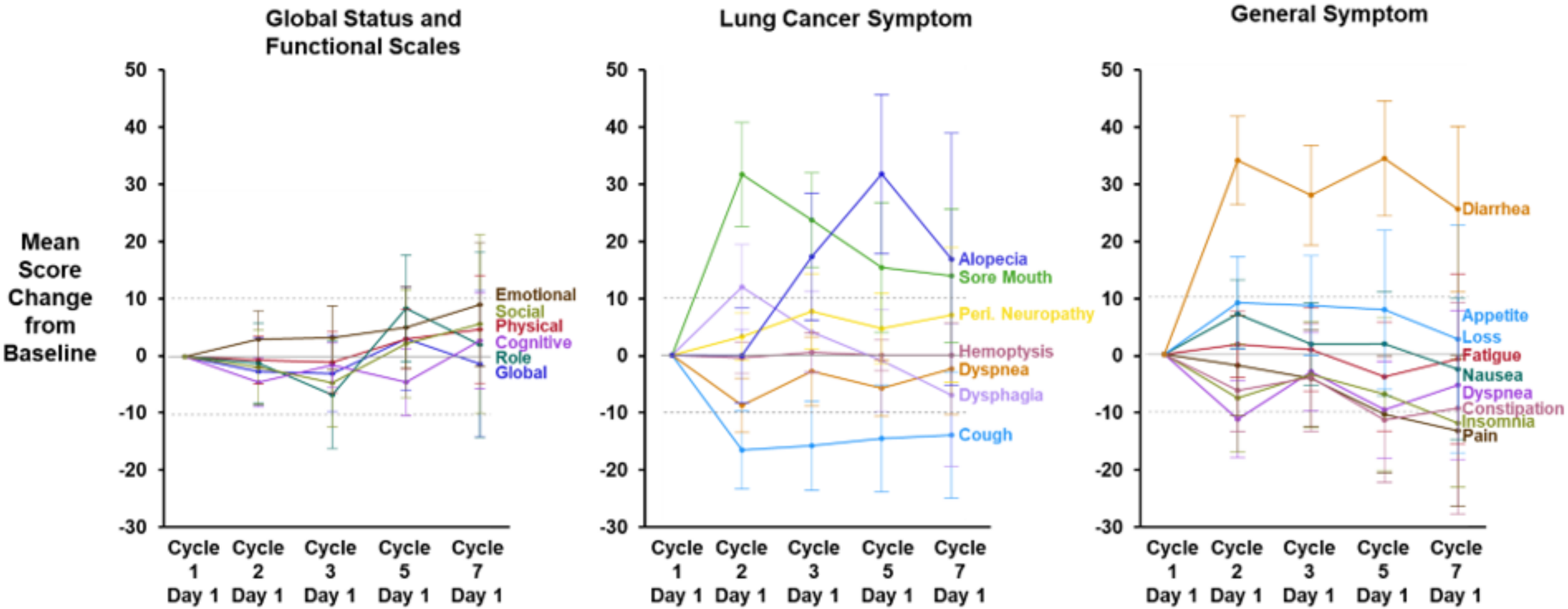
Cohort 2: Poziotinib Active in Brain Metastases

- 14 patients with stable brain lesion(s) identified at baseline

	Patients with Stable Brain Lesions (N = 14)
ORR, % (95% CI)	**28.6%** (8.4, 58.1)
DoR, median months	**5.1**
PFS, median months	**7.4**

NDA data cutoff

Cohort 2: Quality of Life



Number of patients completed QoL were 90, 74, 66, 38, and 25 at Cycle 1, 2, 3, 5, and 7, respectively.

Primary and Supportive Evidence of Poziotinib Efficacy in HER2 Exon 20 Insertion Mutation NSCLC

Primary Efficacy

Study 202 Cohort 2 (N = 90)

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Supportive Efficacy

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MDACC Study 2L HER2 (N = 27)

Previously treated patients with NSCLC harboring HER2 exon 20 insertion mutations

Poziotinib 16 mg QD

Cohort 5: Consistent Efficacy in 16 mg QD Supports Pivotal Cohort 2 Results

HER2, previously treated	Cohort 2 16 mg QD (N = 90)	Cohort 5 16 mg QD (N = 10)
ORR, %	**27.8%**	**40.0%**
95% CI	18.9, 38.2	12.2, 73.8
DoR, median months	**5.1**	**6.5**
95% CI	4.2, 5.5	3.7, NA
PFS, median months	**5.5**	**7.3**
95% CI	3.9, 5.8	5.5, NA

NA = Not available

Cohort 2: NDA data cutoff; Cohort 5: May 16, 2022 data cutoff

Primary and Supportive Evidence of Poziotinib Efficacy in HER2 Exon 20 Insertion Mutation NSCLC

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Supportive Efficacy

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Randomized Dose-Ranging Study

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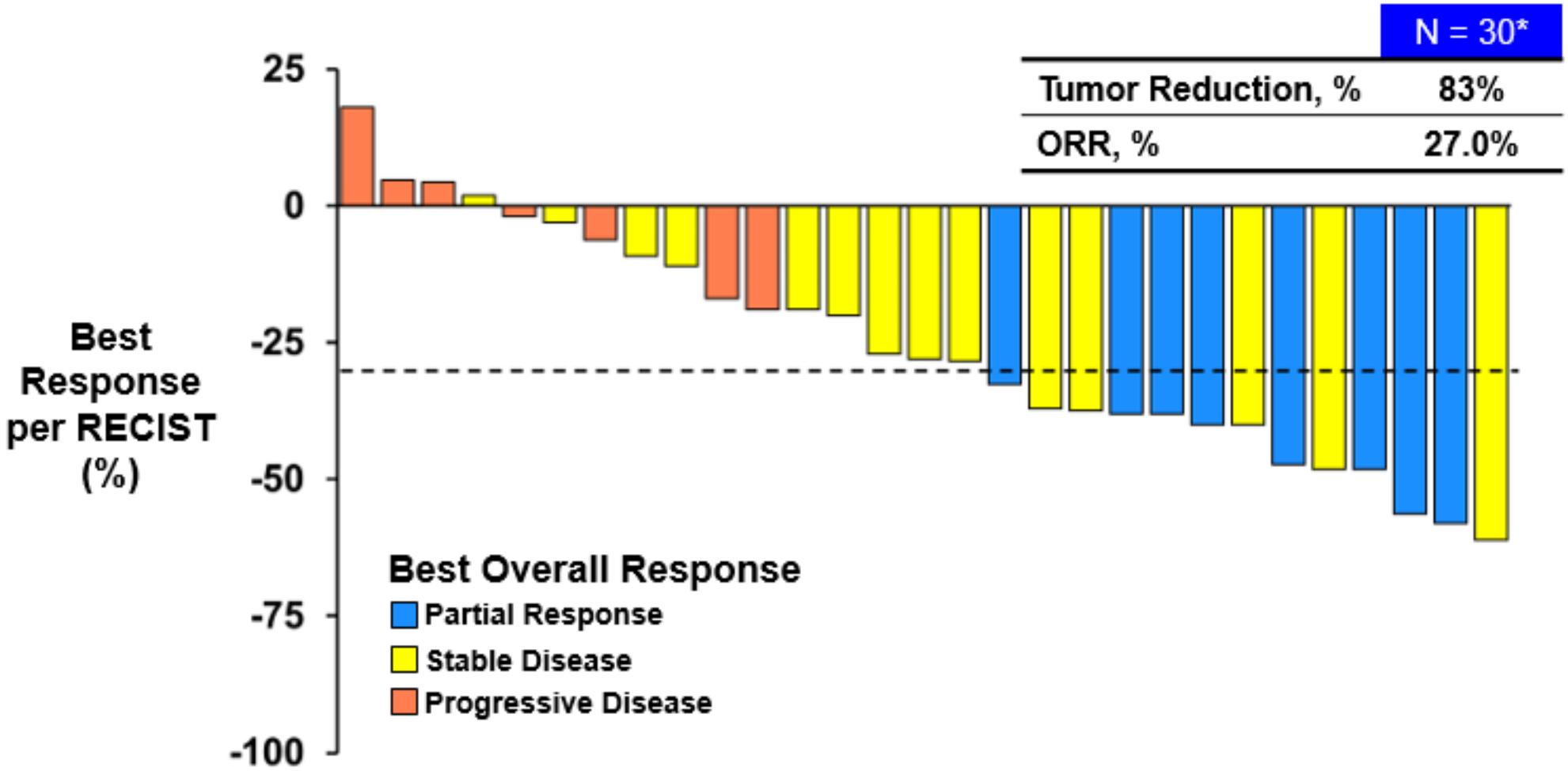
MDACC Study 2L HER2 (N = 27)

Previously treated patients with NSCLC harboring HER2 exon 20 insertion mutations

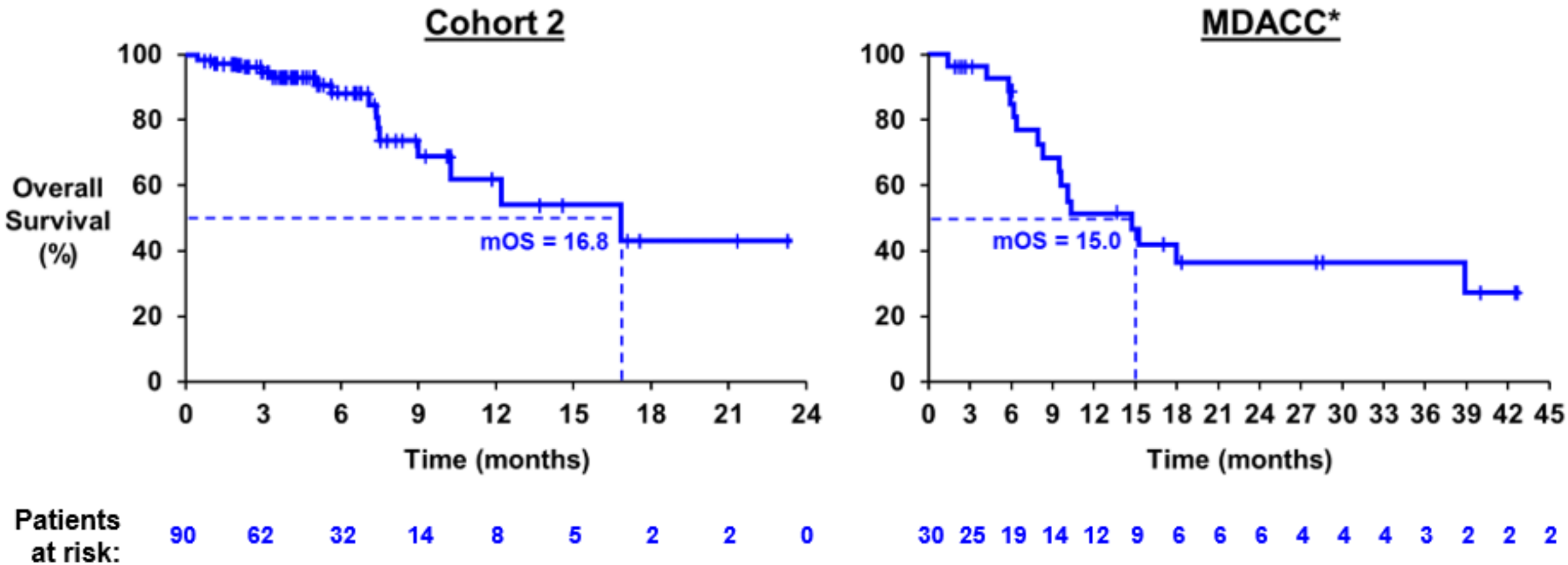
Poziotinib 16 mg QD

MDACC Study Provides Supportive Evidence of Poziotinib Efficacy



*Elamin et al., 2022; Including 3 treatment naïve patients.

Consistent Overall Survival Observed in Cohort 2 and MDACC Studies



*Elamin et al., 2022; Including 3 treatment naïve patients.

Study 202 Cohort 4

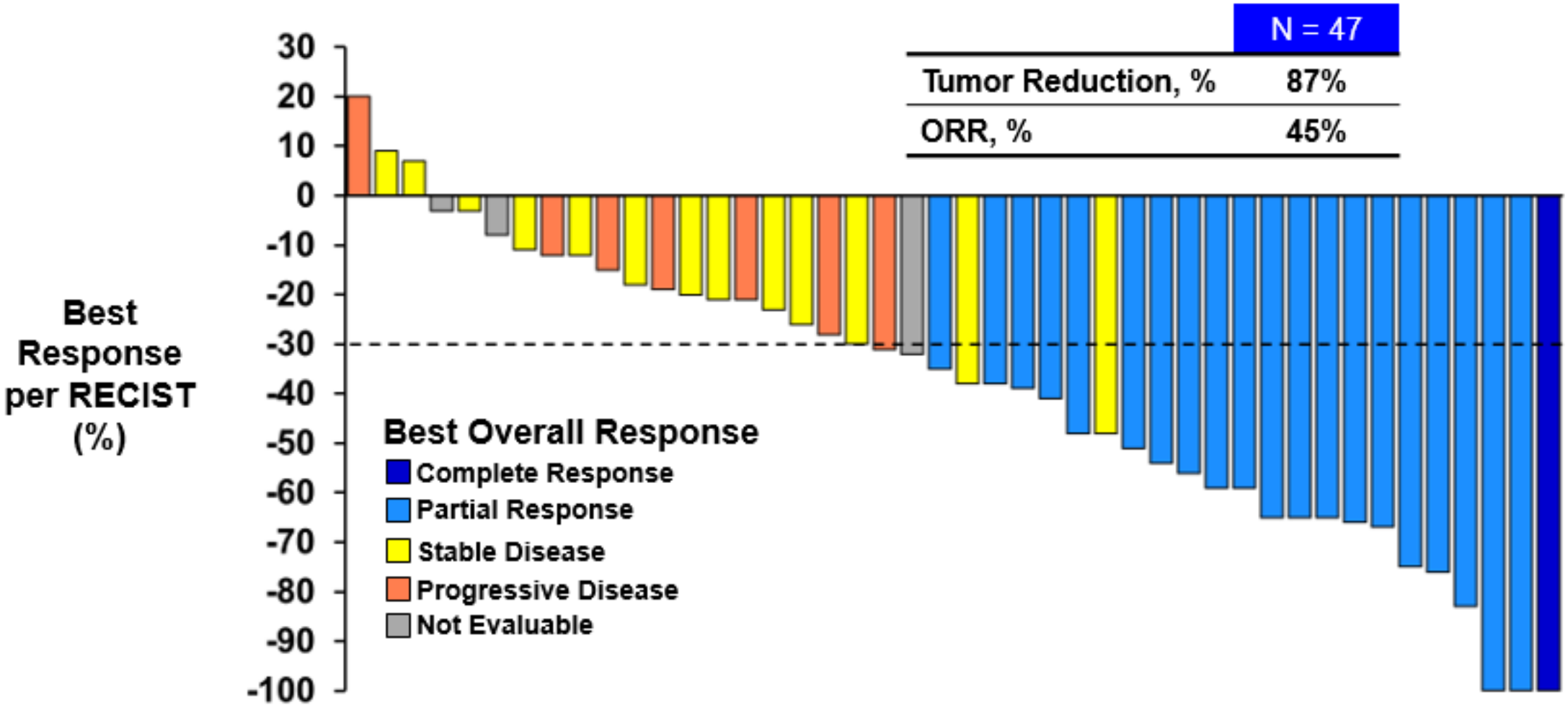
Poziotinib in Treatment-Naïve Patients

Cohort 4: Supportive Poziotinib Efficacy in First-Line Treatment

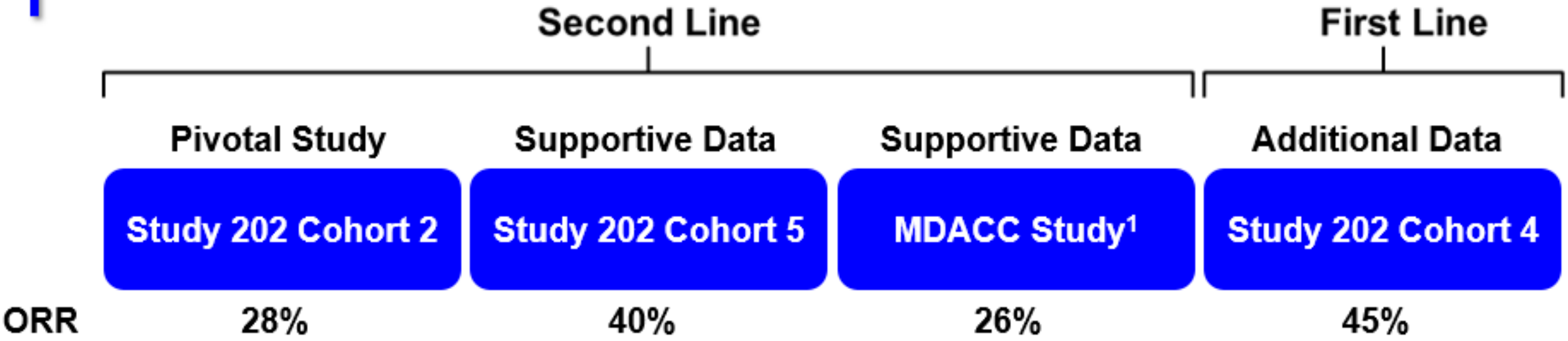
	Poziotinib (16 mg QD) (N = 47)
ORR, n **(%)**	21 **(45%)**
ORR in Evaluable Population (n = 41), n **(%)**	21 **(51%)**
DoR, median (range), months	**5.7** (2.8 – 19.1)
PFS, median (range), months	**5.6** (0 – 22.7+)
DCR, n **(%)**	35 **(74%)**

Analysis from data presented by Sun, et al., 2022 ESMO TAT

Cohort 4: Reduction in Tumor Size



Summary: Poziotinib Demonstrated Clinical Meaningful Benefit to Patients with NSCLC Harboring HER2 Exon 20 Insertion Mutations



- Met prespecified primary endpoint
- Demonstrated clinically meaningful efficacy

- Supports findings from pivotal study

- Encouraging antitumor activity in refractory patients
- Supports findings of pivotal study

- Additional efficacy in efficacy as first-line treatment

Poziotinib showed consistent and reproducible efficacy in the proposed patient population

1. Elamin et al, 2022

Safety

Francois Lebel, MD, FRCPC

Executive Vice President R&D

Chief Medical Officer

Spectrum Pharmaceuticals, Inc.

Study 202: Safety Populations

Cohort 2
(N = 90)

Previously treated patients with NSCLC harboring HER2 exon 20 insertion mutations

Poziotinib 16 mg QD

Group 1
(N = 482)

Patients with NSCLC who received poziotinib

All cohorts who received 16 mg QD or 8 mg BID

Data Cutoff: Nov 19, 2021

Cohort 2: Dose Exposures

	Cohort 2 (N = 90)	Group 1 (N = 482)
Duration of Treatment, median days (min, max)	**113** (1, 972)	**113** (1, 987)
Relative Dose Intensity, median % (min, max)	**72%** (21, 100)	**71%** (2, 118)
Patients with Dose Reduction, n (%)	**69** (77%)	**344** (71%)
Days to First Dose Reduction, median (min, max)	**36** (9, 204)	**34** (1, 362)
Patients with Dose Interruption, n (%)	**78** (87%)	**408** (85%)
Days to First Dose Interruption, median (min, max)	**16** (3, 313)	**16** (2, 313)

Data Cutoff: Nov 19, 2021

Common Adverse Events

Preferred Term, n (%)	Cohort 2 (N = 90)	Group 1 (N = 482)
Any AE	90 **(100%)**	470 **(98%)**
Diarrhea	75 **(83%)**	393 **(82%)**
Rash	62 **(69%)**	287 **(60%)**
Stomatitis	60 **(67%)**	336 **(70%)**
Paronychia	36 **(40%)**	231 **(48%)**
Decreased Appetite	35 **(39%)**	183 **(38%)**
Nausea	35 **(39%)**	180 **(37%)**
Dry Skin	30 **(33%)**	153 **(32%)**
Fatigue	29 **(32%)**	174 **(36%)**
Alopecia	29 **(32%)**	144 **(30%)**
Vomiting	27 **(30%)**	145 **(30%)**

AEs ≥ 30% of Patients
Data Cutoff: Nov 19, 2021

Grade 3 & 4 Adverse Events

Preferred Term, n (%)	Cohort 2 (N = 90)		Group 1 (N = 482)	
	Grade 3	Grade 4	Grade 3	Grade 4
Any AE	77 **(86%)**	10 **(11%)**	328 **(68%)**	39 **(8%)**
Rash	27 **(30%)**	**0**	122 **(25%)**	**0**
Diarrhea	24 **(27%)**	**0**	106 **(22%)**	2 **(0.4%)**
Stomatitis	20 **(22%)**	1 **(1%)**	87 **(18%)**	1 **(0.2%)**
Rash Maculopapular	9 **(10%)**	**0**	39 **(8%)**	**0**
Dermatitis Acneiform	9 **(10%)**	**0**	40 **(8%)**	1 **(0.2%)**

AEs ≥ 10% of Grade 3
Data Cutoff: Nov 19, 2021

Serious Adverse Events

Preferred Term, n (%)	Poziotinib (N = 90)	Group 1 (N = 482)
SAE	36 **(40%)**	193 **(40%)**
Dyspnea	6 **(7%)**	20 **(4%)**
Pneumonia	5 **(6%)**	18 **(4%)**
Pleural Effusion	4 **(4%)**	13 **(3%)**
Pulmonary Embolism	4 **(4%)**	11 **(2%)**
Acute Kidney Injury	4 **(4%)**	10 **(2%)**
Respiratory Failure	4 **(4%)**	6 **(1%)**
Dehydration	3 **(3%)**	12 **(3%)**
Rash	3 **(3%)**	11 **(2%)**
Asthenia	3 **(3%)**	5 **(1%)**
Diarrhea	2 **(2%)**	16 **(3%)**
Hypoxia	2 **(2%)**	6 **(1%)**
Hyponatremia	2 **(2%)**	4 **(0.8%)**
Fatigue	2 **(2%)**	4 **(0.8%)**
Stomatitis	2 **(2%)**	2 **(0.4%)**

Data Cutoff: Nov 19, 2021

Rates of Adverse Events Leading to Permanent Treatment Discontinuation

	Cohort 2 (N = 90)	Group 1 (N = 482)
AE Leading to Discontinuation	21 **(23%)**	85 **(18%)**
Rash	4 **(4%)**	10 **(2%)**
Diarrhea	2 **(2%)**	11 **(2%)**
Paronychia	2 **(2%)**	6 **(1%)**
Stomatitis	2 **(2%)**	6 **(1%)**
Hypoxia	2 **(2%)**	3 **(0.6%)**
Pneumonia	2 **(2%)**	3 **(0.6%)**
Erythema	2 **(2%)**	2 **(0.4%)**
Odynophagia	2 **(2%)**	2 **(0.4%)**
Any treatment-related AE leading to discontinuation	11 **(12%)**	52 **(11%)**

AE leading to discontinuation in ≥ 2% of patients
Data Cutoff: Nov 19, 2021

Pneumonitis / ILD AEs

	N	Any Grade N (%)	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)	Grade 5 N (%)	Median time to first onset (days)
Cohort 2	90	1 (1.1)	1 (1.1)	0	0	0	0	113
Spectrum Group 1 (16 mg QD + 8 mg BID)	482	16 (3.3)	3 (0.6)	3 (0.6)	6 (1.2)	0	4 (0.8)	57
FDA Group 1 (16 mg QD only)	368	12 (3.2)	2 (0.5)	3 (0.8)	4 (1.1)	0	3 (0.8)*	65

*FDA Briefing document refers to 4 deaths (3 16 mg QD + 1 8 mg BID)

Management of Patients During Treatment with Poziotinib

- **Rash**
  - Monitor patients and withhold dose, reduce dose, or permanently discontinue based on severity
- **Diarrhea**
  - Start antidiarrheal agent with initiation of dosing
  - Withhold, reduce dose, or permanently discontinue based on severity
  - Withhold dosing until recovery to less than or equal to Grade 1; then resume poziotinib at same dose or reduced dose depending on severity or reduce poziotinib dose by 2 mg or 4 mg per day
- **Interstitial Lung Disease (ILD) / Pneumonitis**
  - Monitor patients for new or worsening pulmonary symptoms indicative of ILD / pneumonitis
  - Withhold poziotinib for suspected ILD / pneumonitis and permanently discontinue if ILD is confirmed

Off-Target Adverse Events

- No major visceral organ toxicity
- Cardiac Safety
  - No clinically significant abnormal ECGs
  - No QTc prolongation
  - No clinically meaningful changes in cardiac parameters

Safety Summary

- Type of AEs similar to second-generation EGFR TKIs
  - Most common AEs “on-target”: rash, diarrhea, and stomatitis
- Most AEs reversible with recommended supportive medical management or institutional protocols
- Pneumonitis / ILD rarely observed in previously-treated patients with HER2 exon 20 insertion mutations

Poziotinib 16 mg QD Dose Rationale

Extensive Poziotinib Dose / Schedule Assessment in 7 Studies (N = 404)

- Mouse allometric scaling to human was 15 mg QD
- Exploration of doses from 0.5 mg – 32 mg QD
- MTD in Phase 1 studies
  - 18 mg QD daily (continuous) or
    24 mg QD (2 wks on, 1 wk off)
- Continuous dosing appeared to have better clinical activity
- Cohort 5: Randomized dose ranging study confirmed
  16 mg QD as starting dose

Dose Justification for 16 mg QD Starting Dose for HER2 Exon 20

	Cohort 2	Cohort 5		
	16 mg QD (N = 90)	16 mg QD (N = 10)	8 mg BID (N = 40)	12 mg QD (N = 16)
ORR (CR+PR), n **(%)**	25 **(28%)**	4 **(40%)**	9 **(23%)**	4 **(25%)**
DCR (CR+PR+SD), n **(%)**	63 **(70%)**	7 **(70%)**	22 **(55%)**	10 **(63%)**
Median PFS, months	**5.5**	**7.3**	**7.4**	**5.6**

16 mg QD has better efficacy

Cohort 2 Efficacy: March 5, 2021 data cutoff; Cohort 5: May 16, 2022 data cutoff

Tolerance of 16 mg QD Starting Dose for HER2 Exon 20

	Cohort 2	Cohort 5		
	16 mg QD (N = 90)	16 mg QD (N = 10)	8 mg BID (N = 40)	12 mg QD (N = 16)
Any AE	90 **(100%)**	10 **(100%)**	38 **(95%)**	16 **(100%)**
Grade ≥ 3 Treatment-Related AE, n (%)	73 **(81%)**	9 **(90%)**	26 **(65%)**	10 **(63%)**
Grade ≥ 3 Rash	44 **(49%)**	4 **(40%)**	13 **(33%)**	7 **(44%)**
Grade ≥ 3 Diarrhea	23 **(26%)**	2 **(20%)**	5 **(13%)**	2 **(13%)**
Patients with Dose Reduction, n (%)	69 **(77%)**	5 **(50%)**	24 **(60%)**	11 **(69%)**
Patients with Drug Interruption, n (%)	78 **(87%)**	7 **(70%)**	29 **(73%)**	14 **(88%)**

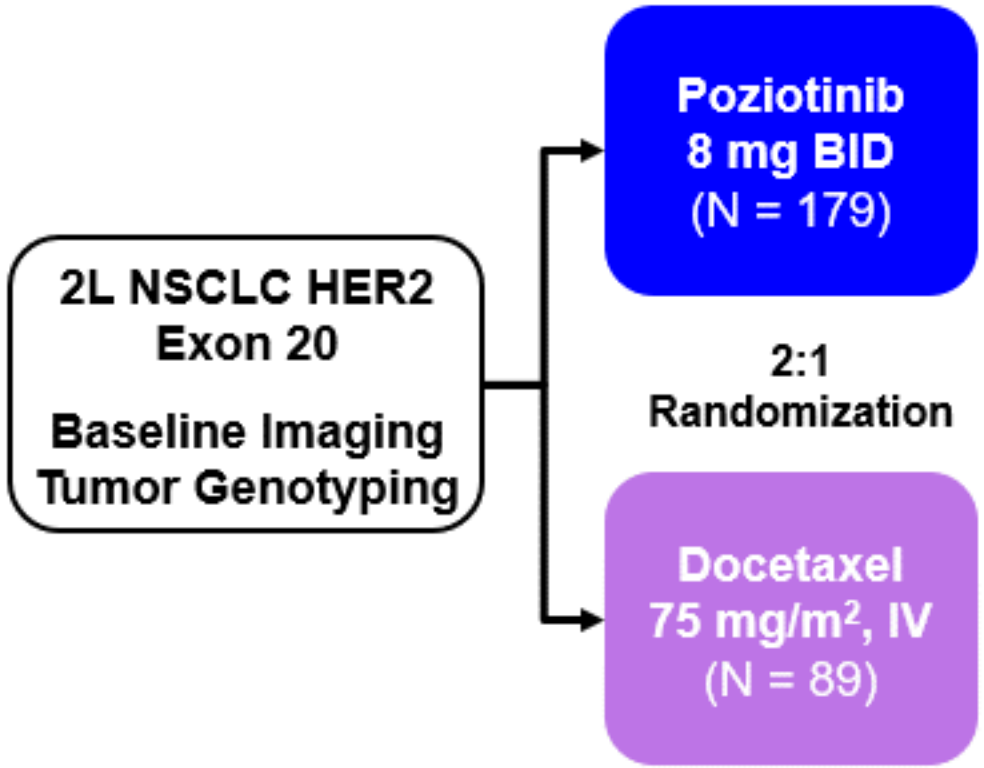
Cohort 2 Safety: Nov 19, 2021 data cutoff; Cohort 5: May 16, 2022 data cutoff

Dose Justification Conclusion

- 16 mg QD is a safe and effective dose
- Extensively studied
  - 7 studies with 404 patients ranging from 0.5 to 32 mg daily
  - 16 mg QD met primary endpoint, tolerated with allowed dose modification
- Urgent medical need for a safe and effective option for patients

Confirmatory Study 301

Study 301: Confirmatory Study Initiated to Confirm Poziotinib Clinical Benefit

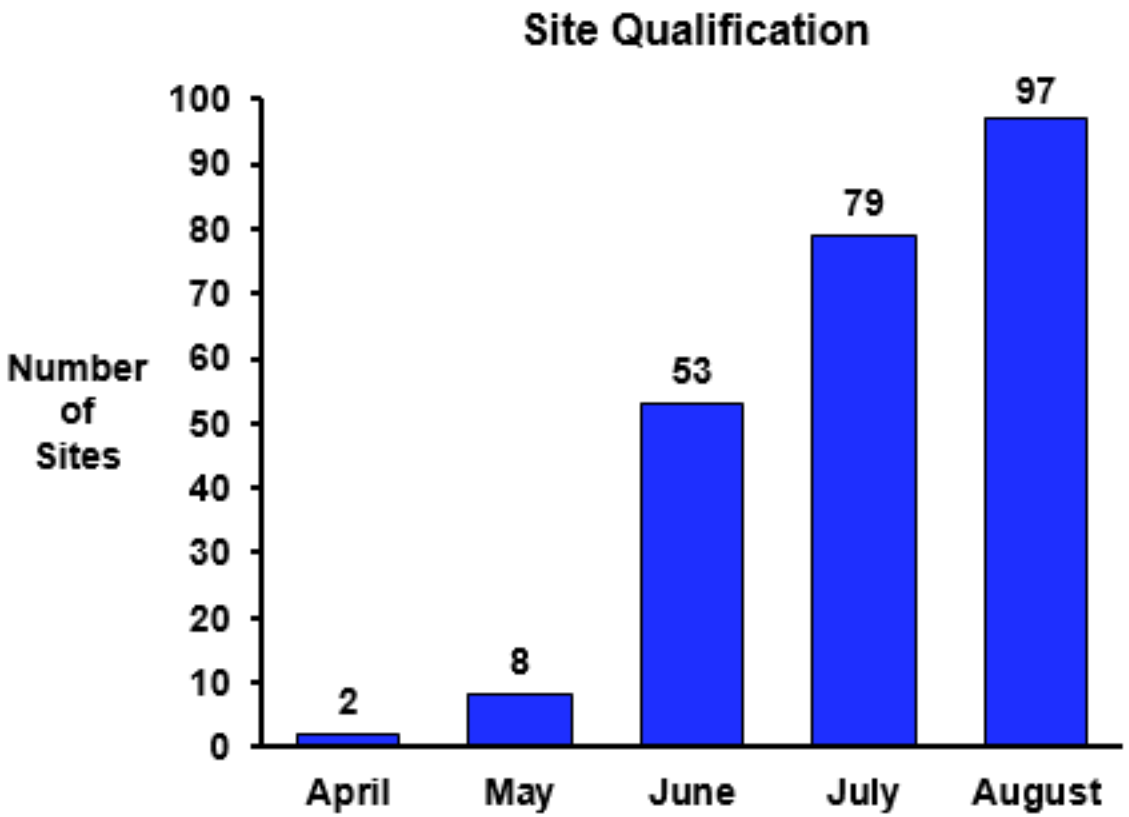


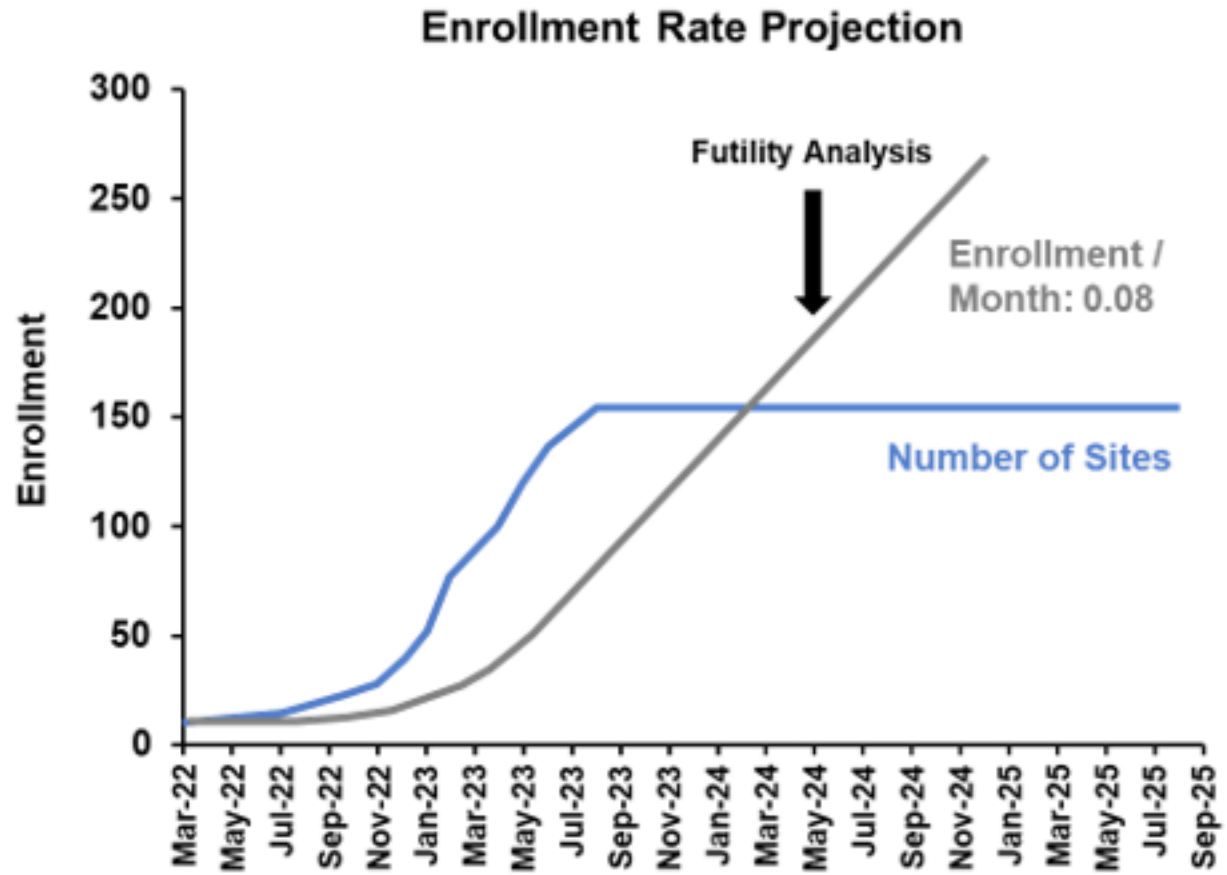
- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, DCR
- Tumor response assessed every 6 weeks by central imaging review
- Designed to enroll 268 patients
- Up to 150 sites globally
- Futility analysis to be conducted in 2024 with 30% event accrual
- Estimated top-line results: 2026

Dose Selection for Study 301 PMR

- Study was originally designed based on the results from Cohort 2 and Stage 1 of Cohort 5 dose ranging study
- Spectrum and FDA agreed on 8 mg BID regimen
- Recent results from Cohort 5 show similar PFS of 7.3 months (16 mg QD) and 7.4 months (8 mg BID)
  - 16 mg QD remains safe and effective
  - 8 mg BID shows a trend of slightly better tolerability

Phase 3 Study Status





Sponsor Position on Key FDA Points

	Sponsor Position
Efficacy	• Unmet need for HER2 Exon 20 NSCLC remains • Poziotinib ORR of 28% is higher than available agents in second line for NSCLC • Met primary efficacy endpoint
Safety	• High rates of Grade 3/4 diarrhea, rash; low permanent discontinuation • Oncologists are medically experienced in handling TKI AEs • Low 0.8% fatal pneumonitis
Dose optimization	• Extensively studied • 7 studies with 404 patients ranging from 0.5 to 32 mg daily • 16 mg QD met primary endpoint, tolerated with allowed dose modification
Confirmatory trial	• Confirmatory study underway at 8 mg BID as agreed with FDA • Sponsor willing to consider protocol amendment • Futility analysis within 2 years

Clinical Perspective

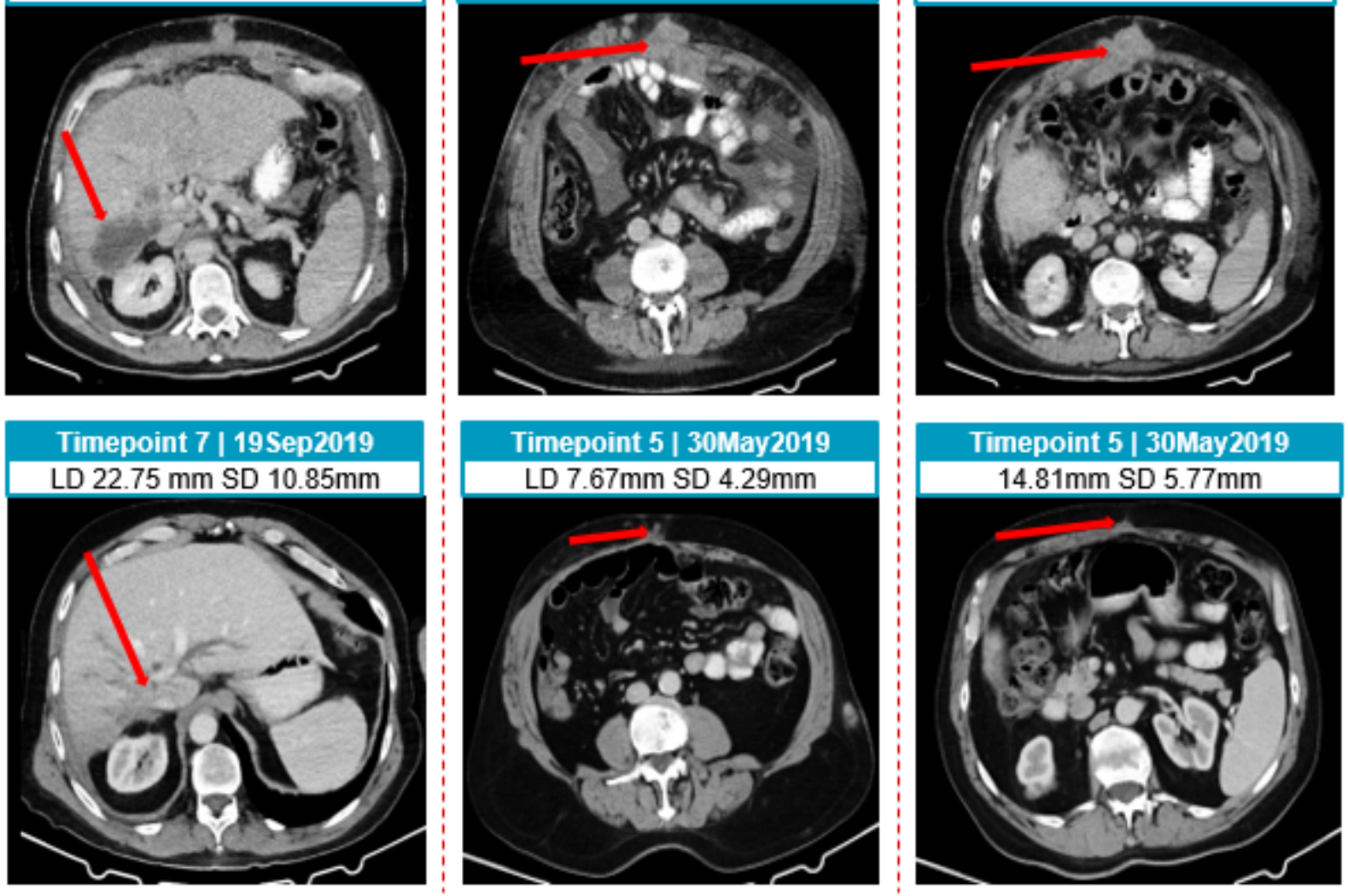
Mark Socinski, MD

Executive Medical Director

AdventHealth Cancer Institute

Cohort 2: Radiographic Response in a Patient Receiving Poziotinib

	Target Lesion 1	Target Lesion 2	Target Lesion 3
Screening	11Dec2018 LD 94.16 mm SD 45.88mm	11Dec2018 32.47mm SD 23.48mm	11Dec2018 LD 36.66mm SD 24.77mm
On-Study Timepoint with Greatest Tumor Reduction	Timepoint 7 | 19Sep2019 LD 22.75 mm SD 10.85mm	Timepoint 5 | 30May2019 LD 7.67mm SD 4.29mm	Timepoint 5 | 30May2019 14.81mm SD 5.77mm



Multiple Targeted Therapies Have Been Approved For 10 Actionable Oncogene Targets in Lung Cancer

EGFR del19 L858R mutations
Erlotinib, gefitinib, afatinib, osimertinib, dacomitinib, erlo+ramucirumab

ALK-rearrangement
Crizotinib, brigatinib, alectinib, ceritinib, lorlatinib

BRAF V600E mutation
Dabrafenib+trametinib

ROS1-rearrangement
Crizotinib, entrectinib

RET rearrangement
Selpercatinib, pralsetinib

NTRK rearrangement
Larotrectinib, entrectinib

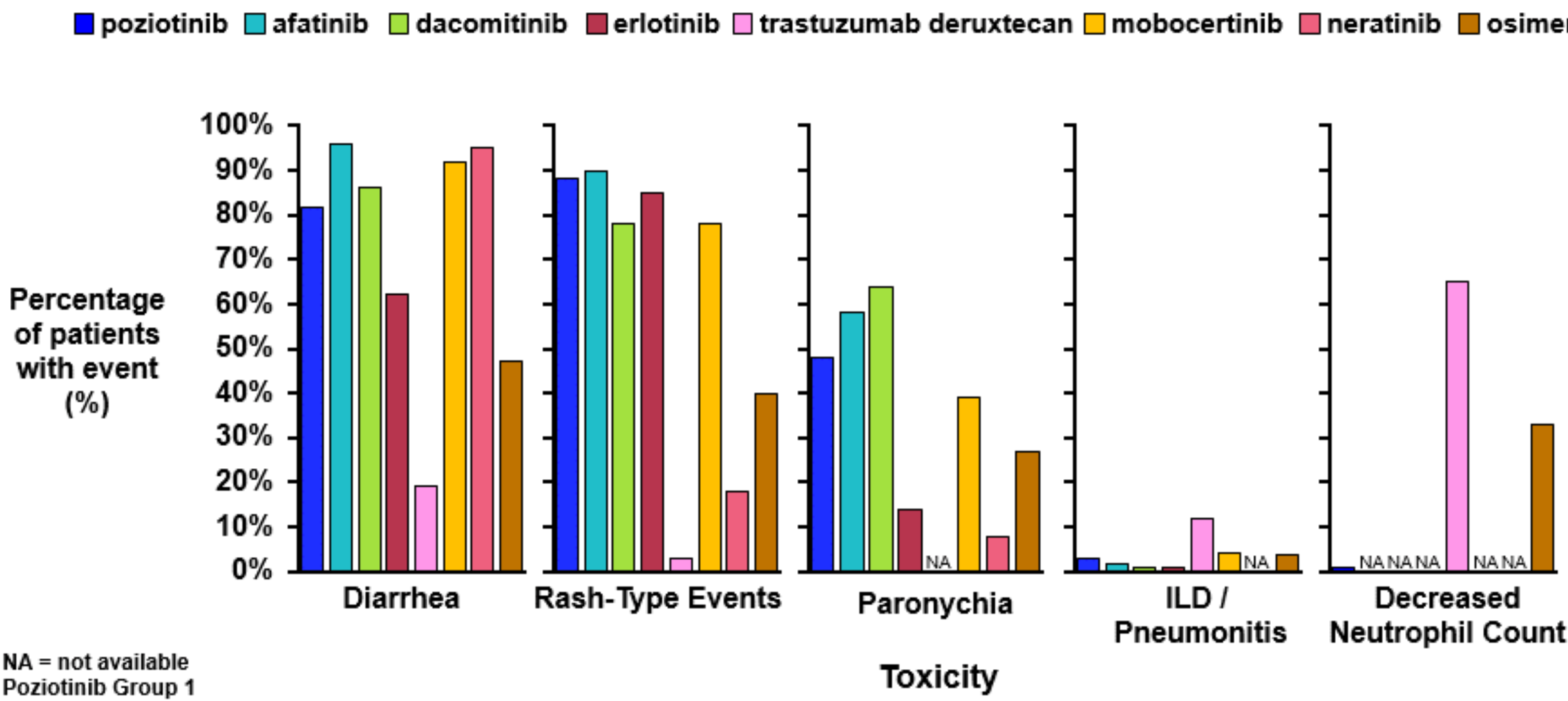
EGFR exon 20 insertion mutations
Mobocertinib, amivantamab

MET exon 14 skipping
Capmatinib, tepotinib

HER2 exon 20 insertion mutations
Fam-trastuzumab-deruxtecan-nxki

KRAS G12C mutation
Sotorasib

Comparison of Toxicities with TKIs and HER2 Targeting ADC (Any Grade)



NA = not available
Poziotinib Group 1
Excerpted from prescribing information accessed Jun & Aug 2022

Important Adverse Reactions with Other Therapies

	Poziotinib	Docetaxel	Trastuzumab deruxtecan	Trastuzumab emtansine
Febrile Neutropenia, %	0	6	1.1	NR
ILD / Pneumonitis, %	1 - 3	NR	12	1
LVEF Reduced	No	No	Yes	Yes
Liver Function Impaired	No	Yes	Yes	Yes

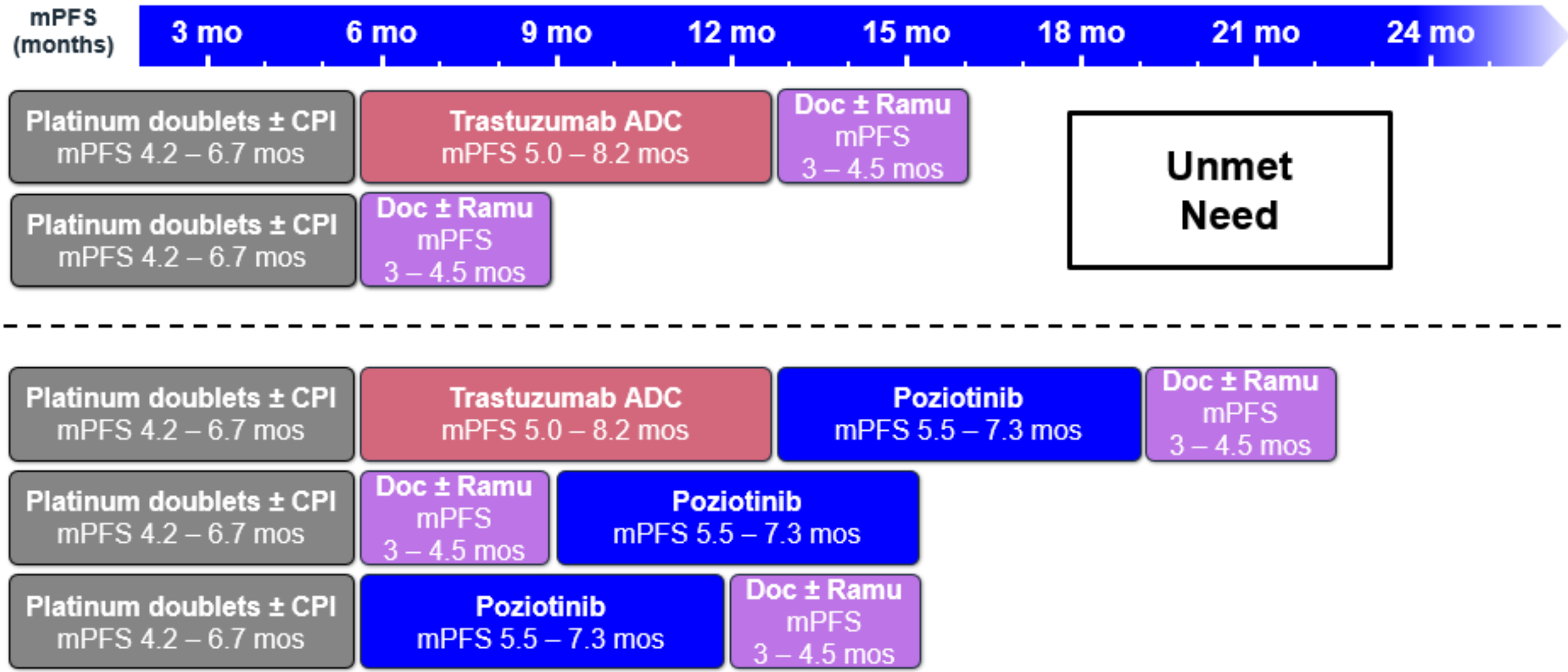
NR = not reported
Excerpted from prescribing information accessed Jun & Aug 2022

Poziotinib Demonstrated Efficacy in All Lines of Therapy

	n / N	ORR, % (95% CI)	DCR, %	mDOR (mos)	mPFS (mos)
Number of Prior Lines of Systemic Therapy					
1 Line	**6 / 27**	**22.2%** (8.6, 42.3)	**66.7%**	**3.9**	**5.4**
2 Lines	**6 / 28**	**21.4%** (8.3, 41.0)	**67.9%**	**6.9**	**6.2**
3+ Lines	**13 / 35**	**37.1%** (21.5, 55.1)	**74.3%**	**5.2**	**5.5**

Poziotinib shows meaningful advantage over available therapies as 2nd plus lines of therapy

Unmet Need for HER2 Exon 20 Insertion NSCLC



Poziotinib Offers Significant Advance for Patients with NSCLC HER2 Exon 20 Mutations

- Demonstrated clinically meaningful efficacy in population with urgent unmet need
- Manageable safety profile similar to other approved TKIs
- Provides a TKI option to overcome chemo resistance
- Provides an oral drug option to seriously ill and remotely located patients
- Provides a positive benefit risk in any 2nd plus lines of therapy

Poziotinib for NSCLC Harboring HER2 Exon 20 Insertion Mutations

Spectrum Pharmaceuticals

Oncologic Drugs Advisory Committee

September 22, 2022

BACK UP SLIDES SHOWN

Study Exclusion Criteria – Pneumonitis/ILD

Poziotinib: Study 202*

Exclusion:

- Grade ≥2 pneumonitis

Trastuzumab deruxtecan: Study DESTINY-Lung02**

Exclusion:

- History of non-infectious interstitial lung disease (ILD)/pneumonitis that required steroids, current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening
- Lung-specific intercurrent clinically significant illnesses including, but not limited to, any underlying pulmonary disorder (eg. pulmonary emboli within three months of the study randomization, severe asthma, severe COPD, restrictive lung disease, pleural effusion, etc.)
- Prior complete pneumonectomy

*POZ-202 Protocol

**ClinicalTrials.gov for DESTINY-Lung02 accessed 09/21/22

Cohort 2 Efficacy: Previously Treated with HER2 Targeted Therapy

Type of Prior Therapy	N	ORR n (%)
PLAT → CPI → HER2	8	1 (12.5)
PLAT → HER2 → CPI	4	1 (25.0)
PLAT → HER2 → TKI (± CPI)	3	2 (67.7)
PLAT → HER2, DOCE (± CPI)	6	1 (16.7)
PLAT → HER2	3	1 (33.3)
HER2	1	0

- 6 patients treated with T-DM1 following platinum therapy, ORR was 33.3% (2/6)

Dose Reductions and Discontinuations Due to AEs – Poziotinib/Other TKIs

	Afatinib	Mobocertinib	Dacomitinib	Poziotinib*
Dose Reductions	57%	25%	66%	51%
Discontinuation	14%	17%	18%	18%

*Group 1, data-cut November 19, 2021

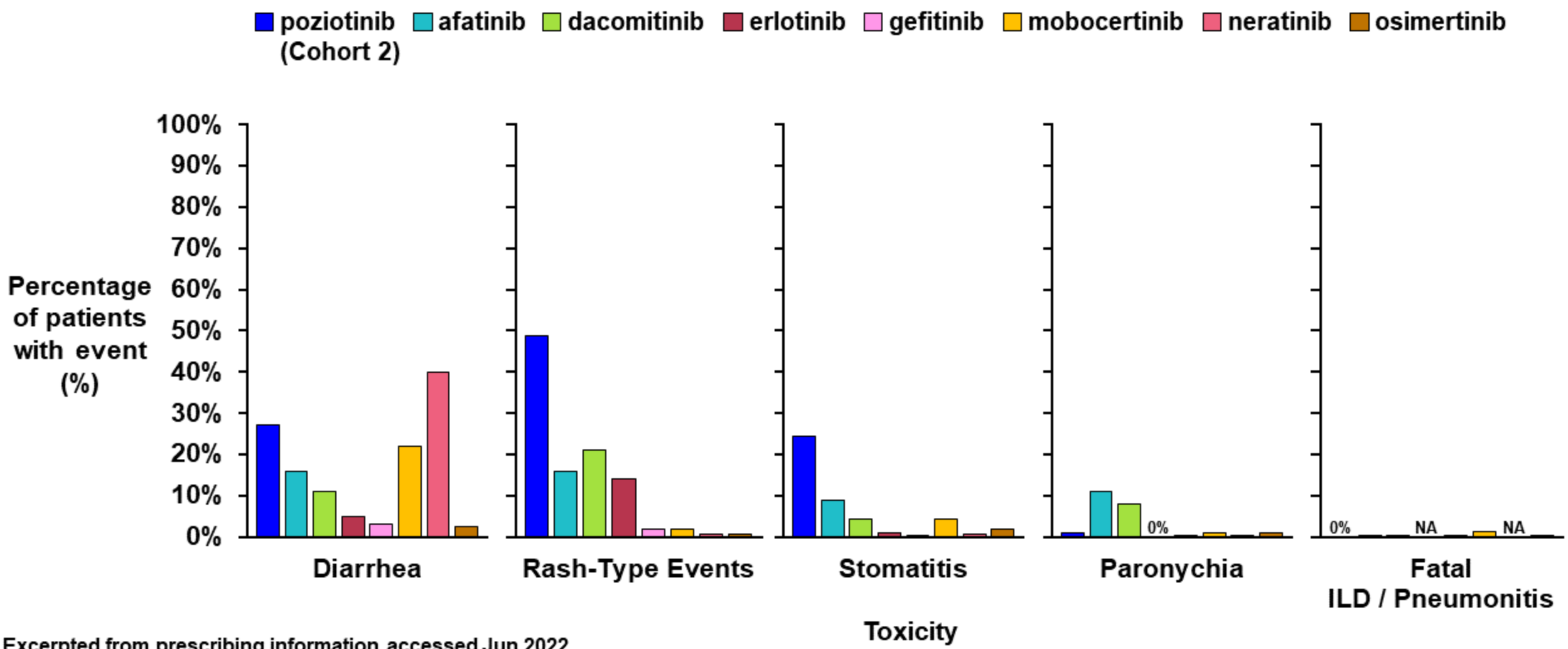
Diarrhea Adverse Events – Comparison with Approved TKIs

	Any Grade	≥ Grade 3	Discontinuation
Poziotinib (N = 482)*	**82%**	**22%**	**2%**
Mobocertinib (N = 114)[1]	**91%**	**21%**	**4%**
Neratinib (N = 141)[2]	**74%**	**22%**	**3%**

*Group 1, data-cut November 19, 2021

1. Zhou et al., JAMA Oncology 2021
2. Hyman et al., Nature 2018

Cohort 2: Comparison of Toxicities with Approved TKIs (Grade ≥ 3)



Excerpted from prescribing information accessed Jun 2022
NA = not available

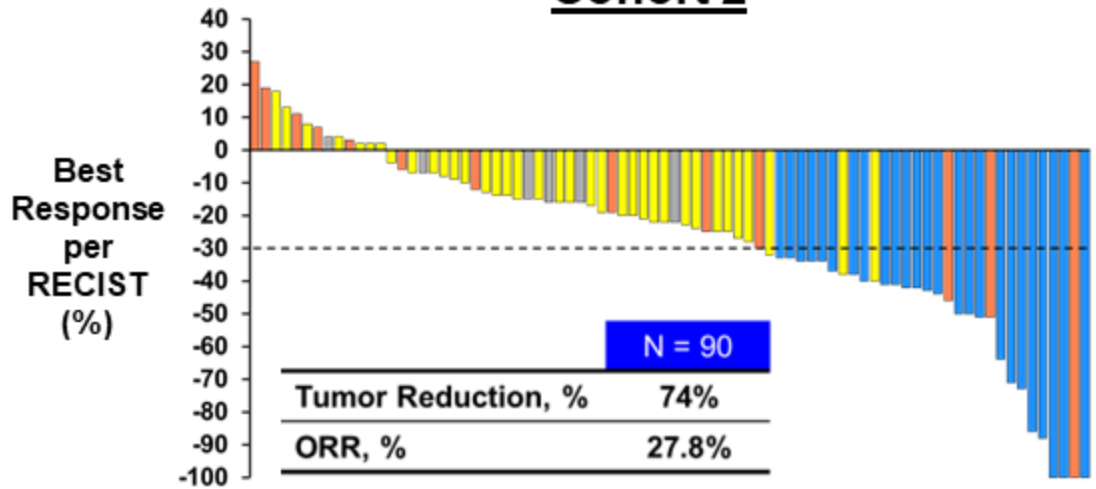
Recent Approvals for Oral Targeted Therapies

Drug (target)	ORR	PFS (months)	N
Poziotinib (HER2 exon20)	28%	5.6	90
Mobocertinib (EGFR exon20)[1]	28%	7.3	114
Sotorasib (KRAS G12C)[2]	28%	5.6	171

1. Zhou et al JAMA Oncol. 2021; 2. Johnson et al ESMO LBA 2022

Poziotinib Efficacy

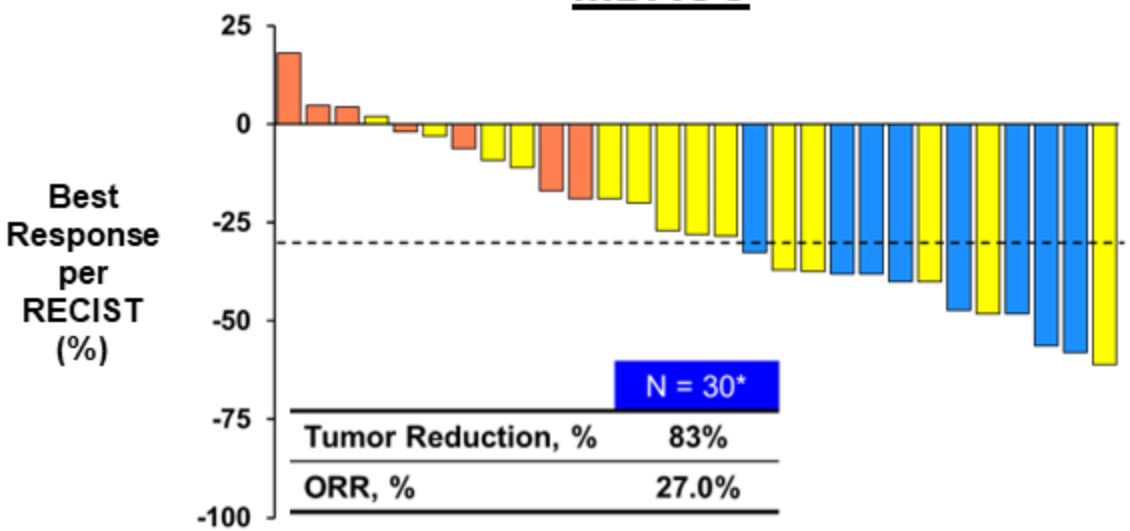
Cohort 2



Best Overall Response

- Complete Response
- Partial Response
- Stable Disease
- Progressive Disease
- Not Evaluable

MDACC



Cohort 4