

A Global Phase 1b Study of ORIC-114, a Highly Selective, Brain Penetrant EGFR and HER2 Inhibitor, in Patients with Advanced Solid Tumors Harboring EGFR and HER2 Exon 20 or HER2 Alterations

Min Hee Hong¹, Alexander Spira², Ki Hyeong Lee³, Eun Kyung Cho⁴, Ji-Youn Han⁵, Byoung-Yong Shim⁶, Jong-Seok Lee⁷, Steven Kao⁸, Sang-We Kim⁹, Adnan Khattak¹⁰, Michael Cheng¹¹, Meenal Patel¹², Rongda Xu¹², Jian Wang¹², Eric Ariazi¹², Anneleen Daemen¹², Edna Chow Maneval¹², Pratik S. Multani¹², Rupal Patel¹², Myung-Ju Ahn¹³

¹Severance Hospital, Yonsei University Health System, Korea; ²VCS Research Institute NEXT Oncology, USA; ³Chungbuk National University Hospital, Korea; ⁴Gachon University Gil Medical Center, Korea; ⁵National Cancer Center, Korea; ⁶The Catholic University of Korea St. Vincent's Hospital, Korea; ⁷Seoul National University Bundang Hospital, Korea; ⁸Chris O'Brien Lifehouse, Australia ⁹Asan Medical Center, Korea; ¹⁰One Clinical Research, Australia; ¹¹University of California at San Francisco, USA; ¹²ORIC Pharmaceuticals, Inc., USA; ¹³Samsung Medical Center, Korea

BACKGROUND

ORIC-114 is a highly selective, brain penetrant, orally bioavailable, irreversible inhibitor designed to selectively target EGFR and HER2 with high potency against exon 20 insertion mutations, making it a promising therapeutic candidate to address the unmet medical need of having both meaningful systemic as well as CNS antitumor activity

STUDY DESIGN

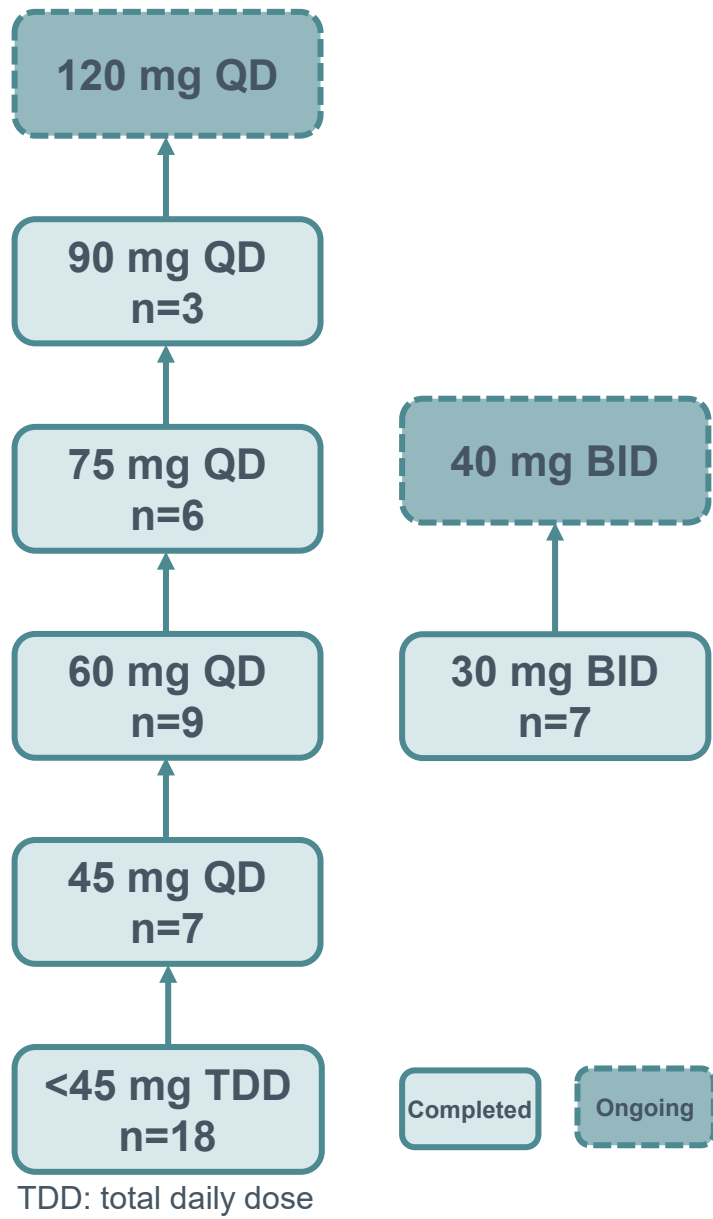
First-in-human, global, multicenter, dose escalation (Part I), followed by dose optimization (Part II), and dose expansion (Phase 2) study (NCT05315700)

PATIENT POPULATION

- Any advanced solid tumor with locally documented:
 - EGFR exon 20 insertion mutation
 - HER2 exon 20 insertion mutation
 - HER2 amplification or overexpression
 - Atypical EGFR mutation (NSCLC only)
- Prior chemotherapy
- All other prior therapies allowed, including prior exon 20 targeted therapies
- RECIST v1.1 measurable disease
- Patients with CNS metastases allowed, including asymptomatic untreated CNS metastases
- ECOG 0-1

OBJECTIVES

- Selection of RP2D and/or MTD
- Overall safety and tolerability as a single agent
- Pharmacokinetics
- Antitumor activity by RECIST v1.1

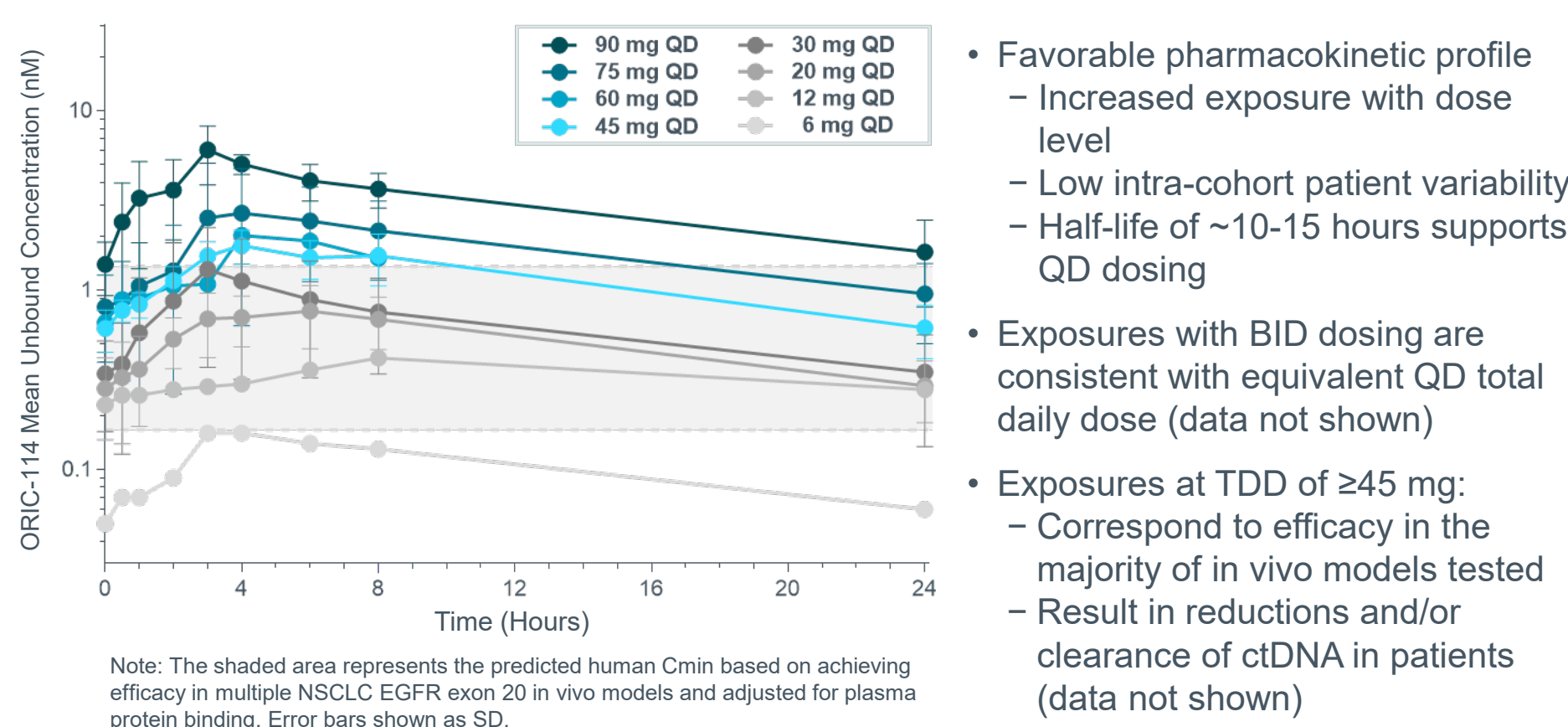


PATIENT CHARACTERISTICS

- As of the data cut-off (26 September 2023), a total of 50 patients were treated with ORIC-114 at increasing doses QD and BID
- Of the patients with EGFR exon 20 insertion mutated NSCLC:
 - 81% were treated with ≥1 prior EGFR exon 20 targeted agent**
 - 19% received multiple EGFR exon 20 targeted agents**
 - 86% presented with CNS metastases at baseline**
- Of the patients with HER2 exon 20 insertion mutated NSCLC:
 - 30% were treated with a prior HER2 targeted agent
 - 38% presented with CNS metastases at baseline

	EGFR Ex20 (n=21)	HER2 Ex20 (n=24)	HER2+ (n=5)	Total (N=50)
Age, years, median (range)	63 (31,80)	63 (25,86)	66 (48,68)	63 (25,86)
Females, n (%)	10 (48)	11 (46)	3 (60)	24 (48)
ECOG performance score, n (%)				
0	1 (5)	10 (42)	3 (60)	14 (28)
1	20 (95)	14 (58)	2 (40)	36 (72)
Non-smoker, n (%)	12 (57)	16 (68)	3 (60)	31 (62)
Prior lines of therapies, median (min, max)	2 (1,6)	2 (0,7)	4 (1,7)	2 (0,7)
Prior therapies, n (%)				
Chemotherapy	21 (100)	23 (96)	5 (100)	49 (98)
EGFR targeted agents	18 (86)	1 (4)	–	19 (38)
EGFR exon 20 targeted agents	17 (81)	–	–	17 (34)
Amivantamab	15 (71)	–	–	15 (30)
Mobocertinib	4 (19)	–	–	4 (8)
Other (CLN-081, BLU-451)	2 (10)	–	–	2 (4)
HER2 targeted agents	–	7 (30)	3 (60)	10 (20)
CNS metastases at baseline, n (%)	18 (86)	9 (38)	1 (20)	28 (56)

ORIC-114 PHARMACOKINETICS



- Favorable pharmacokinetic profile
 - Increased exposure with dose level
 - Low intra-cohort patient variability
 - Half-life of ~10-15 hours supports QD dosing
- Exposures with BID dosing are consistent with equivalent QD total daily dose (data not shown)
- Exposures at TDD of ≥45 mg:
 - Correspond to efficacy in the majority of in vivo models tested
 - Result in reductions and/or clearance of ctDNA in patients (data not shown)

ORIC-114 SAFETY PROFILE

- Well tolerated safety profile with predominantly Grade 1-2 TRAEs at each dose level
- Infrequent dose reductions and discontinuations

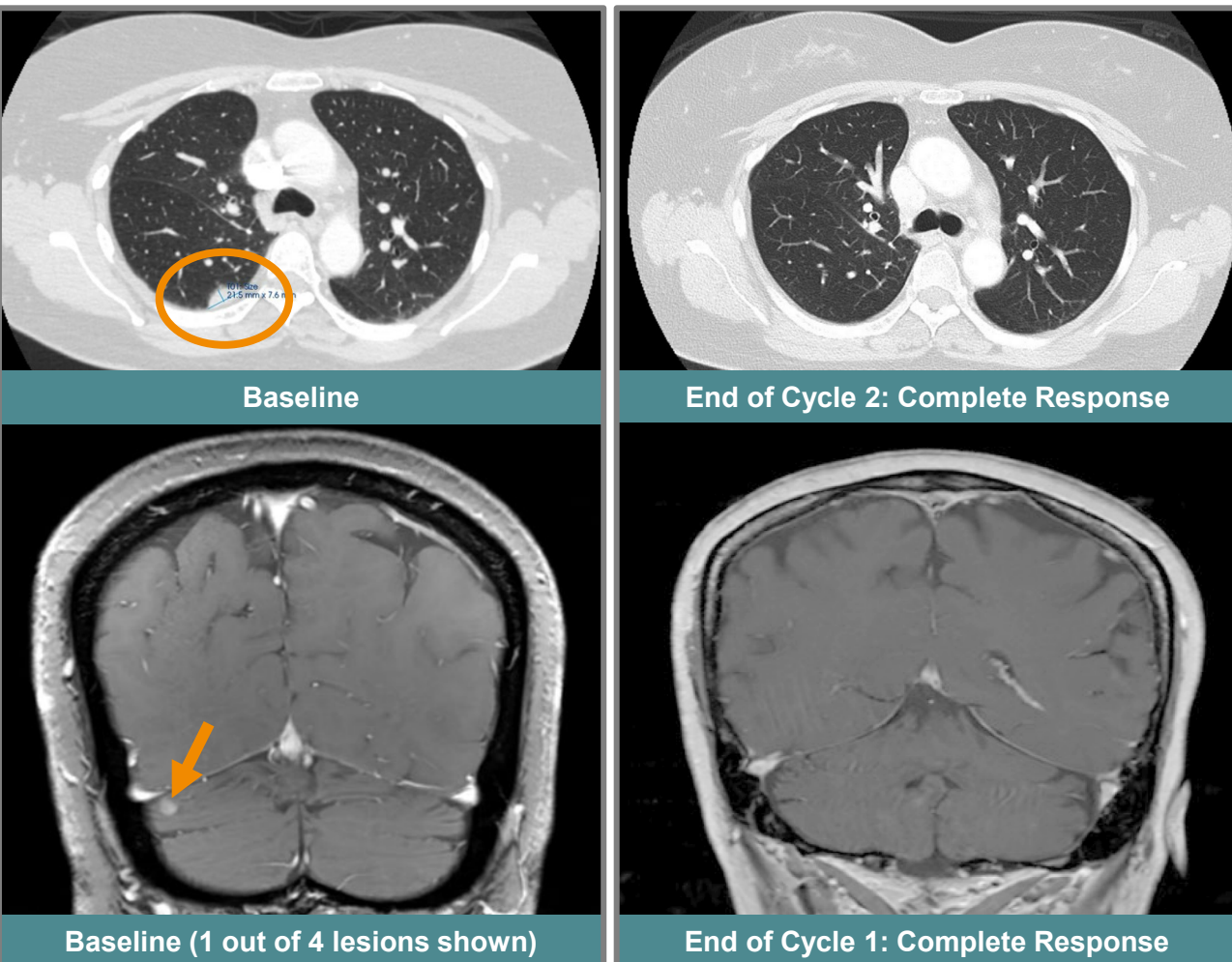
Treatment Related Adverse Events (TRAEs) Occurring in ≥10% of Patients

	<45 mg TDD (n=18)				45 – 60 mg TDD (n=23)				≥75 mg TDD (n=9)				Total (N=50)
Preferred Term, n (%)	Gr1	Gr2	Gr3	≥Gr4	Gr1	Gr2	Gr3	≥Gr4	Gr1	Gr2	Gr3	≥Gr4	All Grades
Rash*	6 (33)	4 (22)	–	–	6 (26)	6 (26)	–	–	4 (44)	1 (11)	–	–	27 (54)
Diarrhea	2 (11)	2 (11)	–	–	7 (30)	2 (9)	2 (9)	–	2 (22)	2 (22)	1 (11)	–	20 (40)
Stomatitis	4 (22)	2 (11)	–	–	2 (9)	2 (9)	1 (4)	–	2 (22)	2 (22)	–	–	15 (30)
Paronychia	1 (6)	2 (11)	–	–	4 (17)	4 (17)	–	–	2 (22)	1 (11)	–	–	14 (28)
Pruritis	2 (11)	–	–	–	4 (17)	2 (9)	1 (4)	–	1 (11)	1 (11)	–	–	11 (22)
Nausea	1 (6)	–	–	–	2 (9)	2 (9)	–	–	1 (11)	1 (11)	1 (11)	–	8 (16)
Decreased appetite	–	1 (6)	–	–	5 (22)	1 (4)	–	–	–	–	–	–	7 (14)
Vomiting	2 (11)	–	–	–	2 (9)	–	–	–	1 (11)	1 (11)	1 (11)	–	7 (14)
Dose Reductions	2 (18)				3 (13)				3 (33)				8 (16)
Dose Discontinuations	1 (9)				1 (4)				–				2 (4)

*Rash includes the following terms: acne, dermatitis, dermatitis acneiform, eczema, hand dermatitis, and rash.

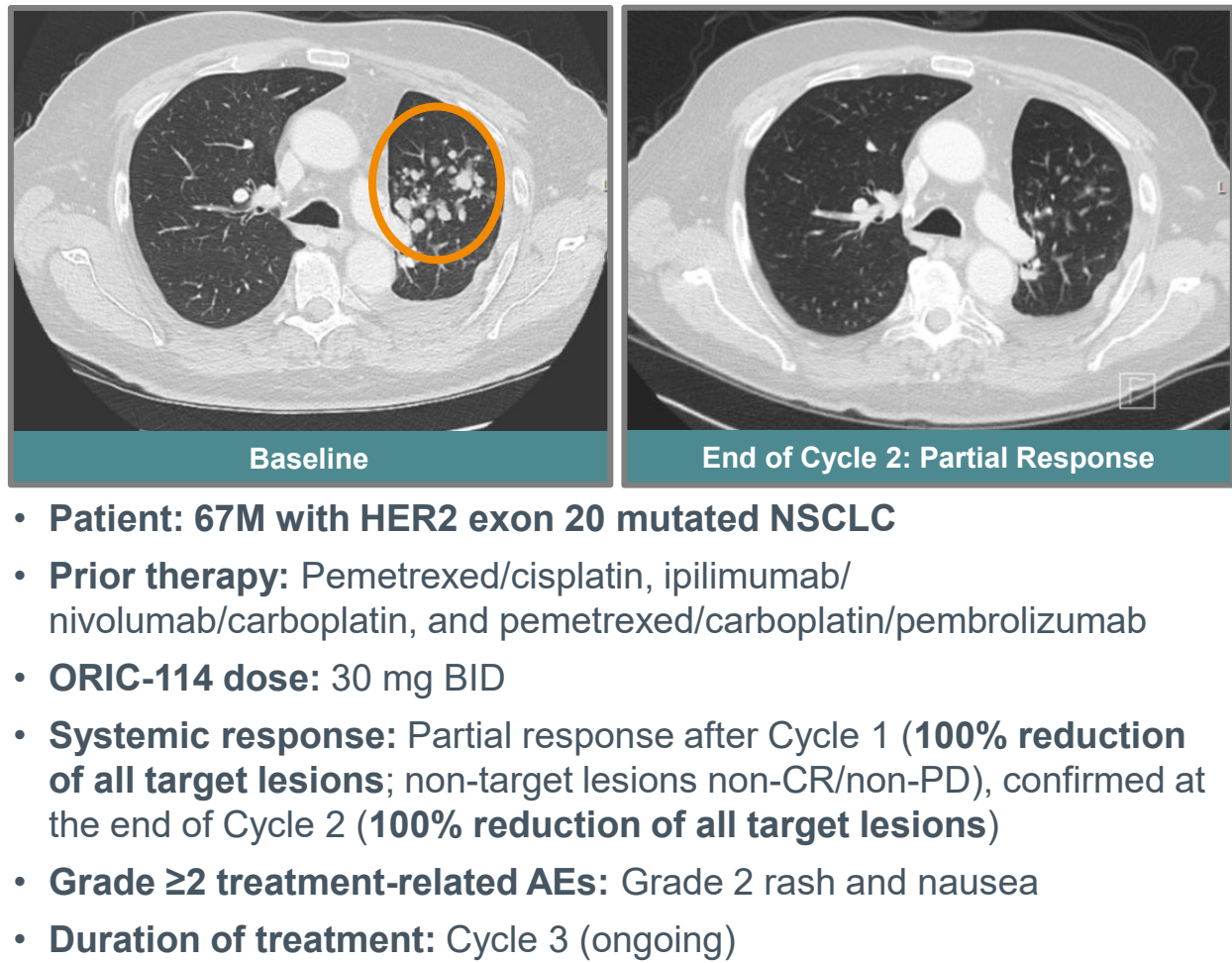
PATIENT VIGNETTES

Confirmed Complete Intracranial and Systemic Response in Patient with EGFR Exon 20 Mutated NSCLC and Active CNS Metastases that Progressed on Prior EGFR Exon 20 Therapy



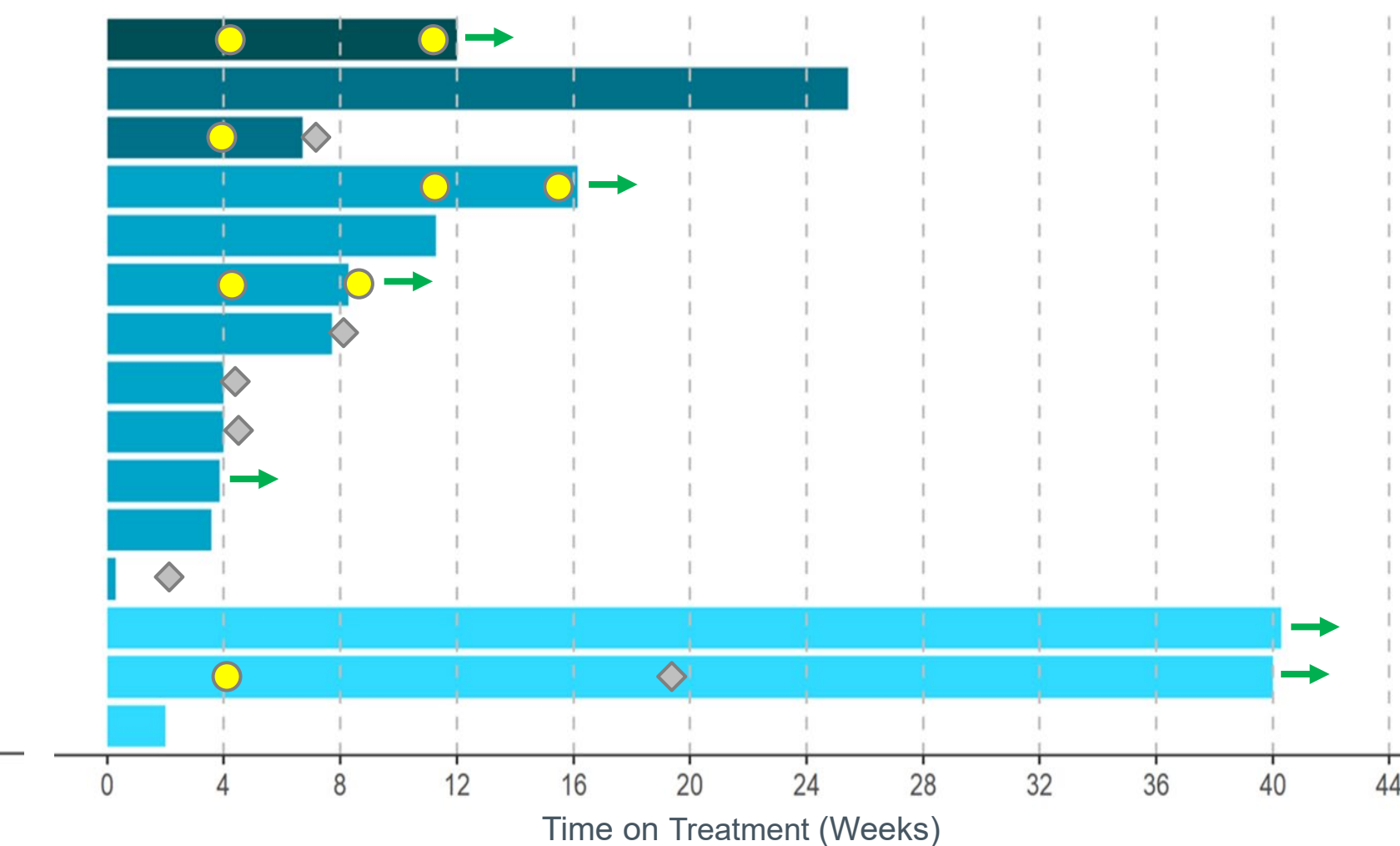
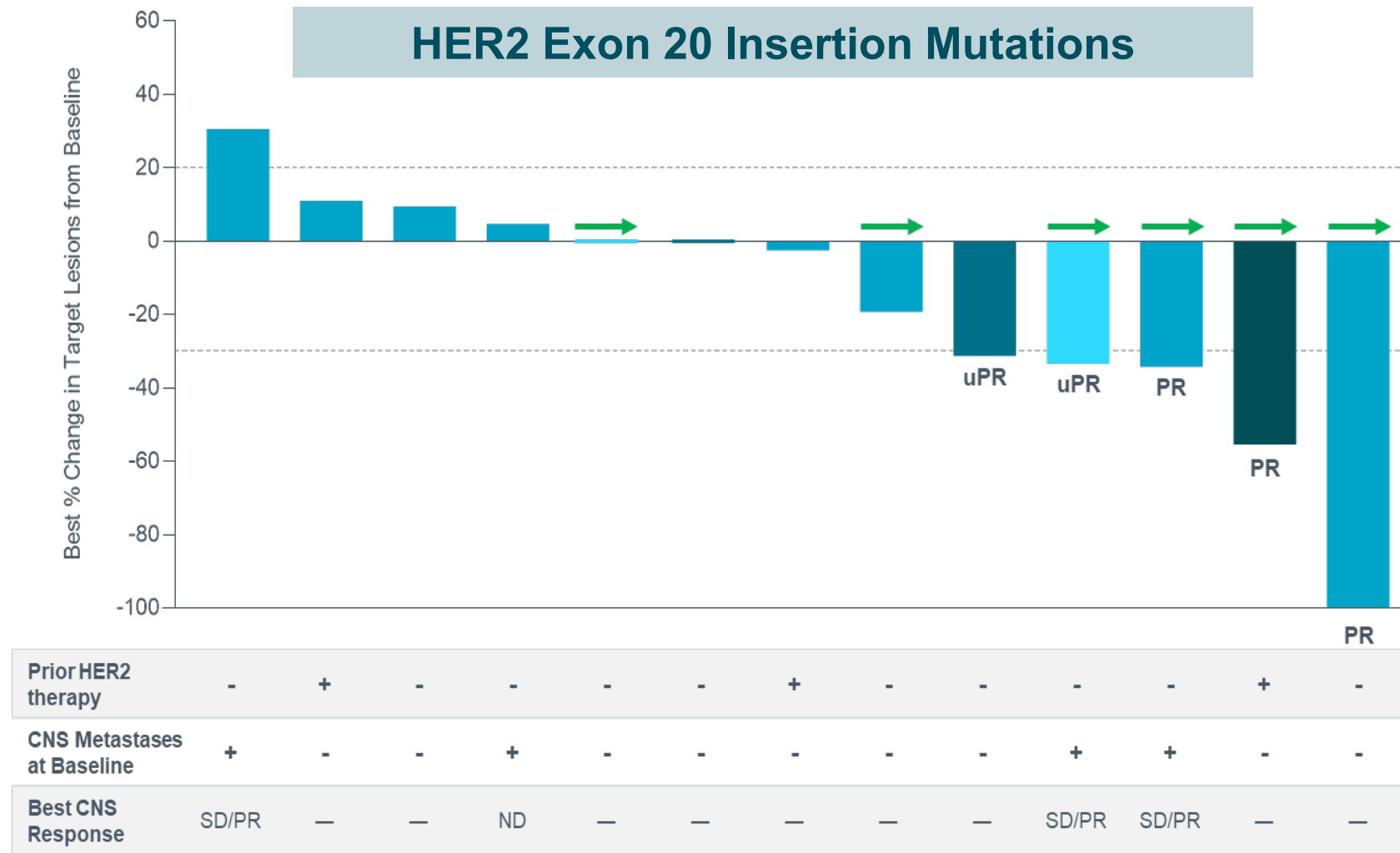
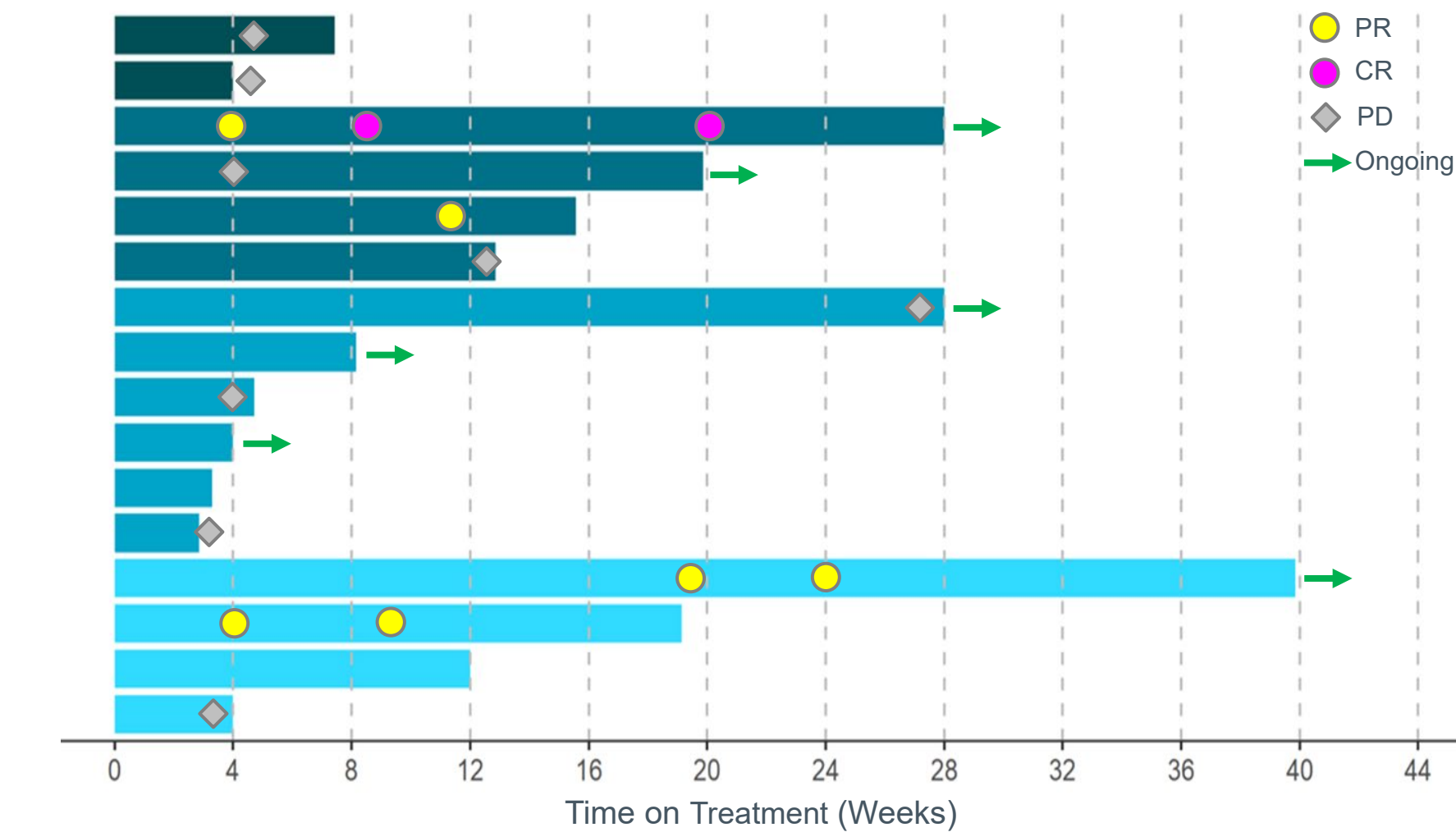
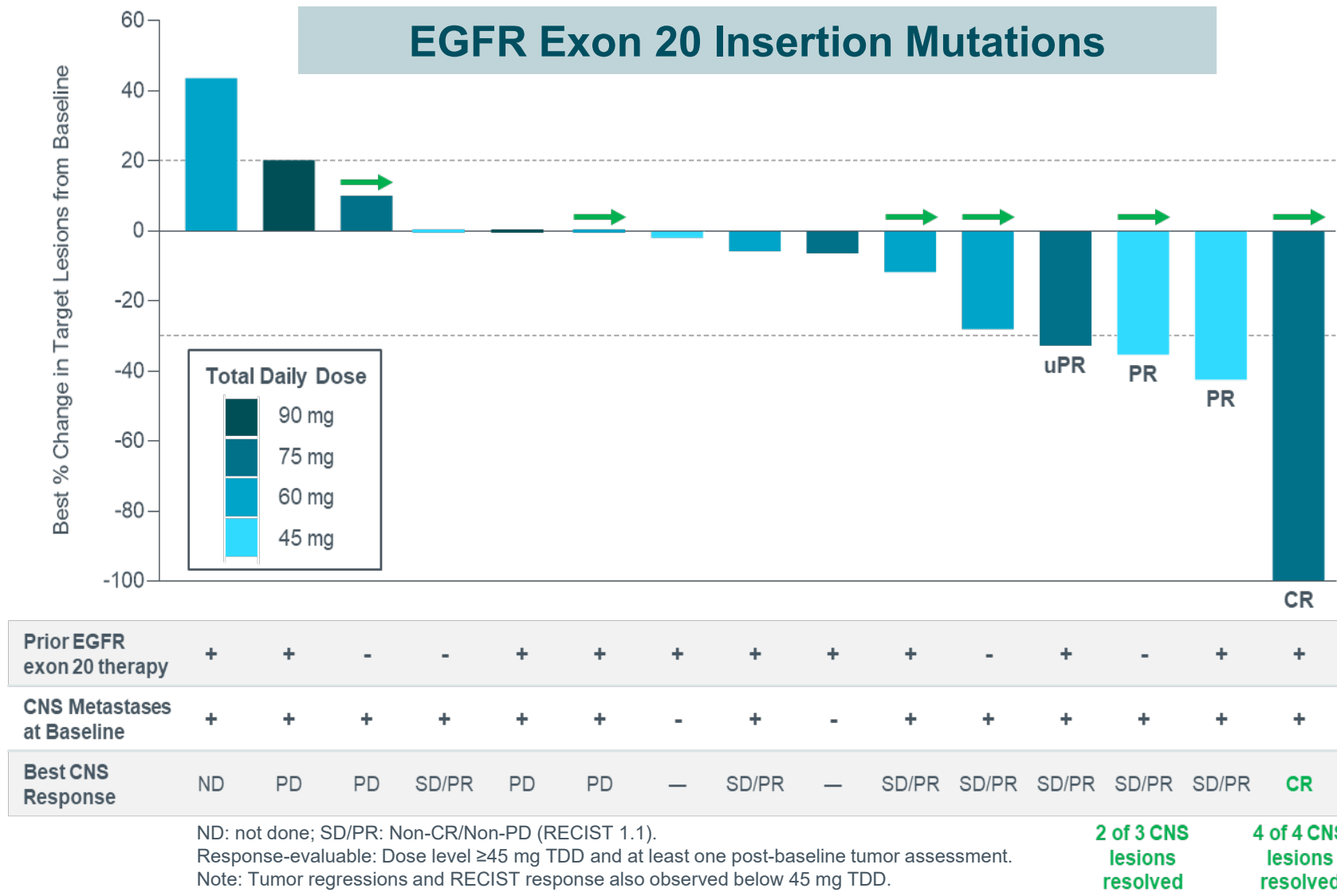
- Patient:** 55F with EGFR exon 20 mutated NSCLC
- Prior therapy:** Pemetrexed/cisplatin and amivantamab
- CNS metastases at baseline:** Four active CNS non-target lesions
 - Previously untreated
 - No prior surgery
 - No prior radiation
- ORIC-114 dose:** 75 mg QD
- Systemic response:** Partial response after Cycle 1 (60% reduction of all target and non-target lesions) followed by complete response at the end of Cycle 2 (**100% reduction of all target and non-target lesions**), subsequently confirmed
- CNS response:** Complete response after Cycle 1 (**100% reduction of all 4 CNS lesions**), confirmed after Cycle 2
- Grade ≥2 treatment-related AEs:** Grade 2 mucositis and paronychia
- Duration of treatment:** Cycle 9 (ongoing)

Confirmed 100% Regression of Target Lesions in Patient with HER2 Exon 20 Mutated NSCLC



- Patient:** 67M with HER2 exon 20 mutated NSCLC
- Prior therapy:** Pemetrexed/cisplatin, ipilimumab/nivolumab/carboplatin, and pemetrexed/carboplatin/pembrolizumab
- ORIC-114 dose:** 30 mg BID
- Systemic response:** Partial response after Cycle 1 (**100% reduction of all target lesions**; non-target lesions non-CR/non-PD), confirmed at the end of Cycle 2 (**100% reduction of all target lesions**)
- Grade ≥2 treatment-related AEs:** Grade 2 rash and nausea
- Duration of treatment:** Cycle 3 (ongoing)

ORIC-114 ANTITUMOR ACTIVITY IN EXON 20 INSERTION MUTATED NSCLC PATIENTS



CONCLUSIONS

- ORIC-114 is a highly selective, brain penetrant, orally bioavailable, irreversible inhibitor that selectively targets EGFR and HER2 with high potency against exon 20 insertion mutations and atypical EGFR mutations (Poster #1345P)
- ORIC-114 has a clinical half-life that supports QD dosing and is well tolerated across all doses
- The safety profile of ORIC-114 consists mainly of Grade 1 and 2 adverse events with little evidence of off-target toxicities
 - The most common TRAEs were low grade rash and diarrhea, with only 6% G3 diarrhea and no ≥G3 rash
- In this patient population with an exceptionally high rate of prior exon 20 targeted therapies and CNS disease at baseline compared to other reported data sets, early antitumor activity has been observed at all total daily doses of 45 to 90 mg in patients with EGFR and HER2 exon 20 mutated NSCLC, including in patients with active CNS metastases at baseline
 - Complete systemic and CNS response has been demonstrated in a patient with prior EGFR exon 20 targeted therapy
 - Multiple responses were observed in additional patients with EGFR exon 20 mutated NSCLC, most previously treated with exon 20 targeted therapies
 - Multiple responses were observed in patients with HER2 exon 20 mutated NSCLC
- Given the observed wide therapeutic index, dose escalation continues with higher QD and BID doses to select provisional RP2Ds for dose optimization