Poziotinib administered twice daily improves safety and tolerability in patients with EGFR or HER2 exon 20 mutant NSCLC (ZENITH20-5)

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Poziotinib is an investigational drug not approved by the FDA

2021 AACR Virtual Annual Meeting Plenary Clinical Trial Abstract: #5176

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Introduction

- Effective treatment for patients with metastatic non-small cell lung cancer (mNSCLC) harboring EGFR or HER2 exon 20 insertion mutations represents an important unmet medical need.[1]
- Poziotinib is a potent, irreversible, tyrosine kinase inhibitor (TKI) targeting EGFR and HER2 exon 20 insertion mutations.[2-4]
- The safety and efficacy of once daily (QD) dosing with poziotinib at 16mg QD has been established previously in a large, multicentric study with blinded central image review.[5]
- Poziotinib has a short half-life of 7.2 hours allowing for twice daily (BID) dosing in order to reduce Cmax and associated toxicity.
- Preliminary safety with poziotinib administered BID dosing has been recently presented at 2021 ESMO TAT in patients treated for EGFR and HER2 exon 20 NSCLC suggesting improved tolerability.
- Here we present updated safety and preliminary efficacy of BID dosing.

Material and Methods

- ZENITH20 (NCT03318939) is a Phase 2, open-label, multi-cohort, multi-center study designed to evaluate the efficacy and the safety/tolerability of poziotinib in previously treated and treatment-naïve patients with NSCLC.
- The ongoing ZENITH20-Cohort 5 enrolls patients with locally advanced or mNSCLC with EGFR or HER2 exon 20 insertion mutations.
- Patients are being randomized to various arms: 10, 12, and 16 mg QD or 6 and 8 mg BID.
- Dose reductions are allowed in the presence of toxicity and patients are treated until death, disease progression or intolerable toxicity.

Entry Criteria

Inclusion Criteria

- Histologically or cytologically confirmed NSCLC which is locally advanced or metastatic
- Documented EGFR or HER2 exon 20 insertion mutation by a tissue next generation sequencing test
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- Stable CNS metastases are allowed

Exclusion Criteria

- Previously treated with poziotinib or any other EGFR or HER2 exon 20 insertion mutation-selective TKI
- EGFR exon20 point mutation

Figure 1. ZENITH20: a Phase 2 multi-cohort international trial

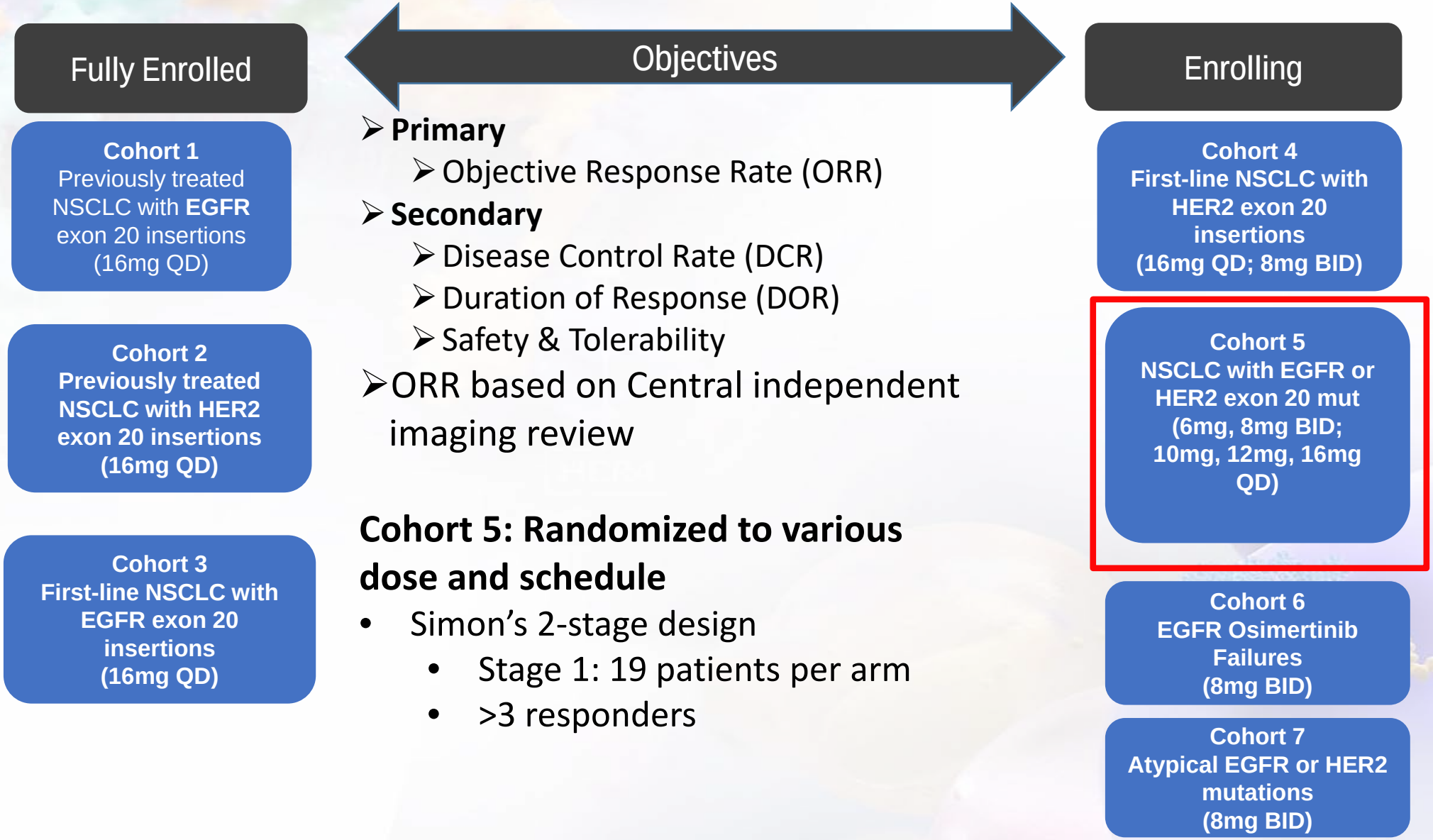


Table 1. Demographics and Baseline Characteristics

	16mg QD (N=26)	8mg BID (N=31)	12mg QD (N=25)	6mg BID (N=32)	10mg QD (N=37)
Median age, yrs (range)	62.5 (44, 78)	66 (34, 82)	66 (42, 76)	58 (23, 82)	64 (37, 87)
Gender: female / male	19 / 7	19 / 12	19 / 6	19 / 13	28 / 9
ECOG Status: 0 / 1	7 / 19	13 / 18	7 / 18	11 / 21	11 / 26
Prior platinum and CPI exposure, n (%)	12 (46)	11 (35)	12 (48)	12 (38)	20 (54)
Receptor status: EGFR / HER2	16 / 10	23 / 9	9 / 16	20 / 12	22 / 15

NA = data not available

Initial Cohort 5 randomized to 10mg or 12mg or 16mg QD; amended to randomized to 6 or 8mg BID or 10mg QD

Table 2. Patient Disposition

Disposition, n (%)	16mg QD N=26	8mg BID N=31	12mg QD N=25	6mg BID N=32	10mg QD N=37
Ongoing	10 (38)	21 (68)	8 (32)	23 (72)	13 (35)
Discontinued	16 (62)	10 (32)	17 (68)	9 (28)	24 (65)
Adverse Event	0	2 (6)	1 (4)	1 (3)	2 (5)
Disease Progression	5 (19)	3 (10)	7 (28)	2 (6)	15 (41)
Death	2 (8)	1 (3)	3 (12)	3 (6)	3 (8)
Withdrew consent	5 (19)	3 (10)	4 (16)	2 (6)	2 (5)
Other	4 (15)	1 (3)	2 (8)	1 (3)	2 (5)

Data cutoff date: 5 Mar 2021

Table 3. ≥Grade 3 Related Adverse Events of Special Interest

Adverse Event, n (%)	16mg QD N=26	8mg BID N=31	12mg QD N=25	6mg BID N=32	10mg QD N=37
≥Grade 3 related AEs	13 (50)	8 (26)	11 (44)	5 (16)	18 (49)
Diarrhea	4 (15)	4 (13)	3 (12)	1 (3)	8 (22)
Rash	6 (23)	4 (13)	10 (40)	2 (6)	11 (30)
Stomatitis	5 (19)	5 (16)	1 (4)	2 (6)	2 (5)
Paronychia	0	0	0	0	0
Pneumonitis	0	0	0	0	0
Grade 5 related AE	0	0	0	0	0

Table 4. Drug Interruptions and Reductions

	16mg QD N=22	8mg BID N=18	12mg QD N=23	6mg BID N=20	10mg QD N=35
Drug interruption, n (%)	18 (82)	13 (72)	20 (87)	10 (50)	24 (69)
Median days to first interruption	13	16	18.5	28.5	29.5
Dose reduction, n (%)	13 (59)	9 (50)	13 (57)	9 (45)	12 (34)
Median days to first reduction	30	18	35	45	57.5

Denominator is the number of patients with dosing data from patient diary for at least one cycle

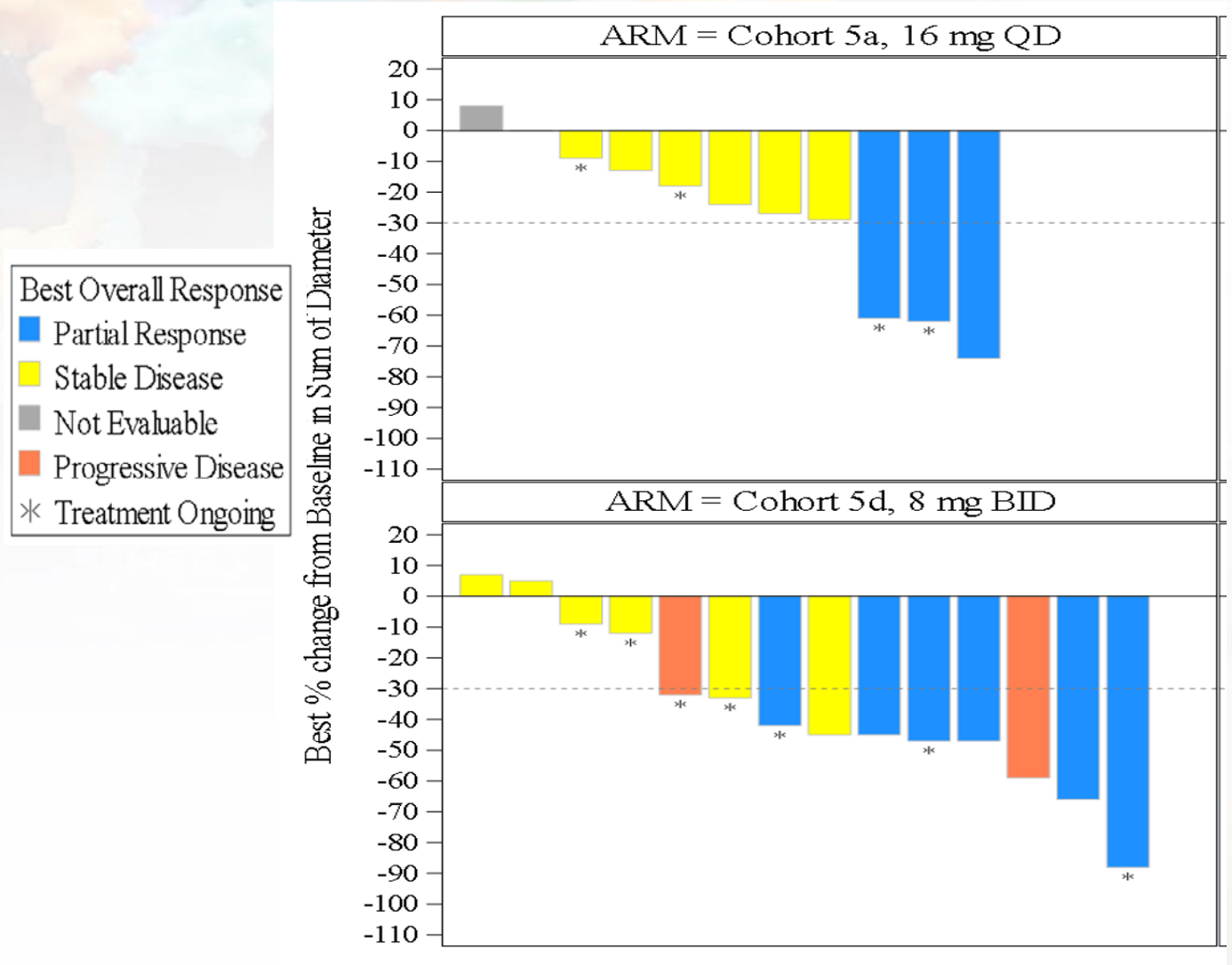
Table 5. Preliminary Efficacy

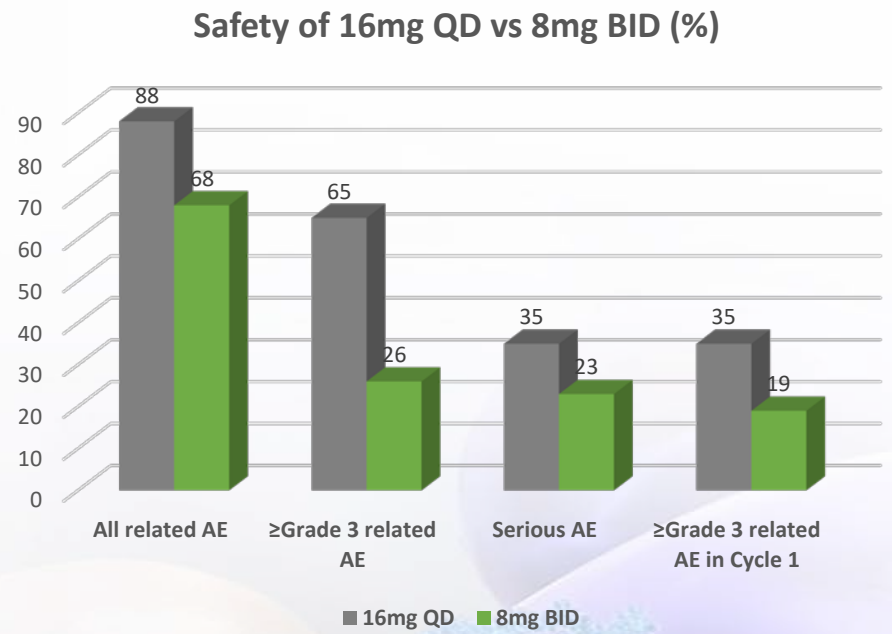
	16mg QD (N=19)	8mg BID (N=19)	12mg QD (N=19)	6mg BID (N=19)	10mg QD (N=19)
Overall Response Rate, n (%)	**3 (15.8)**	**6 (31.6)**	**3 (15.8)**	**1 (5.3)**	**1 (5.3)**
PR - Partial Response	3 (15.8)	6 (31.6)	3 (15.8)	1 (5.3)	1 (5.3)
SD - Stable Disease	7 (36.8)	7 (36.8)	9 (47.4)	12 (63.2)	8 (42.1)
PD - Progressive Disease	0	2 (10.5)	3 (15.8)	1 (5.3)	7 (36.8)
NE- Not Evaluable (withdrawn)	9 (47.4)	4 (21.1)	4 (21.1)	5 (26.3)	3 (15.8)
Disease control Rate, n (%)	**10 (52.6)**	**13 (68.4)**	**12 (63.2)**	**13 (68.4)**	**9 (47.4)**

Response evaluated using blinded central image review using RECIST v1.1

- The 10mg QD starting dose was well tolerated but has shown suboptimal anti-tumor activity with higher rate (37%) of disease progression. This dosing arm has been discontinued.

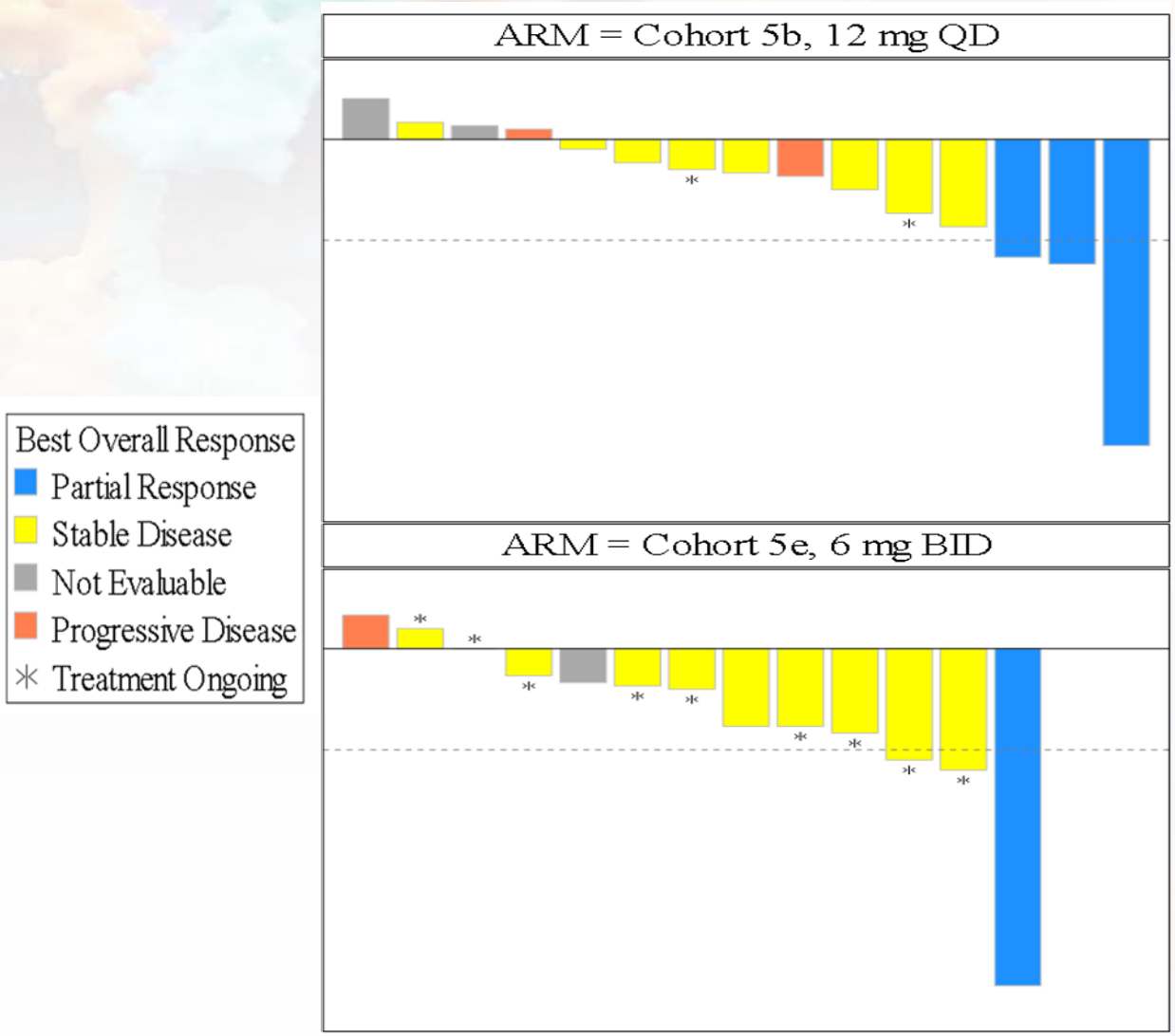
Figure 2. Efficacy – Safety Comparison of 16mg QD vs 8mg BID

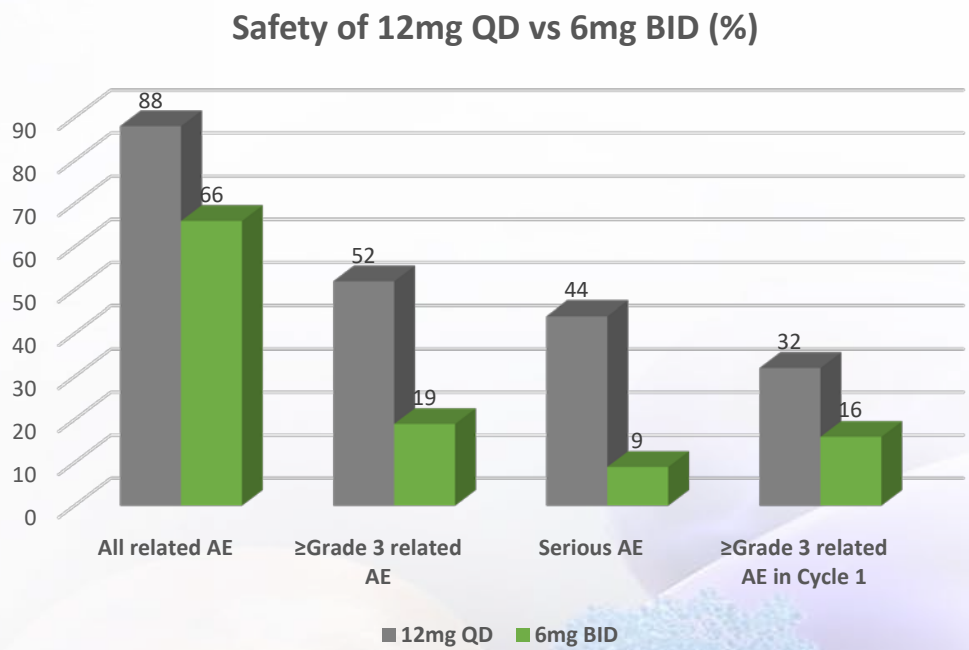




Patients not evaluable for tumor measurement are not included in the waterfall plot

Figure 3. Efficacy – Safety Comparison of 12mg QD vs 6mg BID





Patients not evaluable for tumor measurement are not included in the waterfall plot

Conclusions

- Poziotinib demonstrates improved tolerability with BID vs QD dosing at both 8mg and 6mg BID
  - Reduced treatment emergent ≥Grade 3 AEs and treatment-related AEs
  - Reduced dose interruptions
- Preliminary response data shows improved anti-tumor activity with 8mg BID dosing compared to 10, 12, 16mg QD or 6mg BID
  - ORR of 31.6% over previously reported EGFR and HER2 cohorts at 16mg QD
- Cohort 5 Stage 2 is currently enrolling at 8mg BID

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Acknowledgments

- We thank all the patients and their families
- We thank all the ZENITH20 investigators and the study teams at each participating center