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KontRASt-01 update: Safety and efficacy of JDQ443 in *KRAS G12C*-mutated solid tumors including non-small cell lung cancer (NSCLC)

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SUMMARY

- JDQ443 is a structurally unique KRAS[G12C] inhibitor that exhibits antitumor activity in NSCLC
  - Preliminary ORR: 57.1% (8/14) at recommended DEx of 200 mg BID
- JDQ443 is well tolerated and has an acceptable safety profile
  - TRAEs were low-frequency, low-grade events
    - No grade 4 to 5 TRAEs
    - No nausea, vomiting, or diarrhea higher than grade 2
    - ALT/AST grade 2 to 3 elevation events were rare and of limited duration
  - Safety/tolerability profile supports potential for combination strategies
- The KontRASt clinical trial program continues to evaluate JDQ443 monotherapy and combinations in patients with advanced *KRAS G12C*-mutated solid tumors
  - Ongoing KontRASt studies: KontRASt-01, KontRASt-02, KontRASt-03, and KontRASt-06

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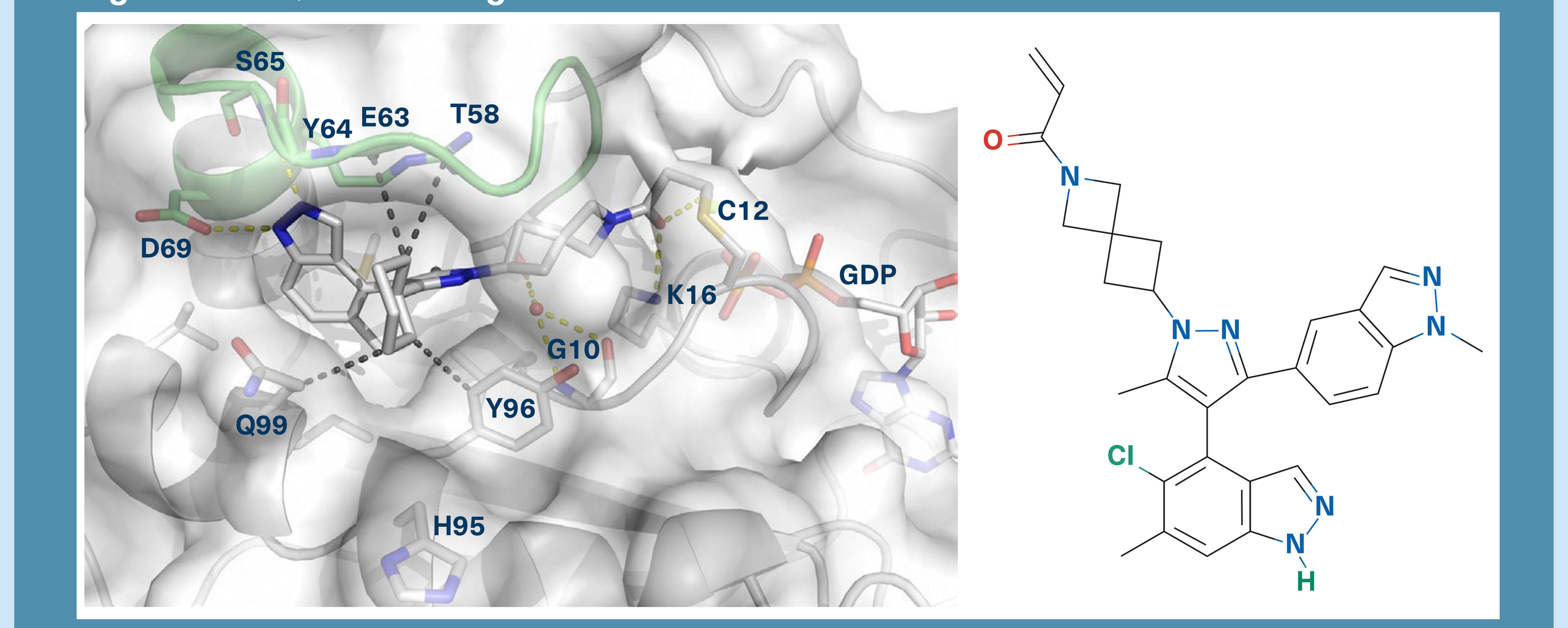
Previously presented at Multidisciplinary Thoracic Cancers Symposium (November 30-December 2, 2023; New Orleans, LA; abstract 100) and American Society of Clinical Oncology Annual Meeting (June 2-6, 2023; Chicago, IL, and Online; abstract 9007).

BACKGROUND

- Constitutive activation of Kirsten rat sarcoma viral oncogene homolog (KRAS) guanosine triphosphate (GTP)ase by gain-of-function mutations, such as *KRAS G12C*, acts as an oncogenic driver in solid tumors, including NSCLC[1-4]
- JDQ443 is a selective and potent, covalent, structurally novel, orally bioavailable KRAS[G12C] inhibitor that binds to KRAS[G12C] in the guanosine diphosphate (GDP)-bound state and demonstrates potent and selective preclinical efficacy[5-7] (**Figure 1**)
- In the Phase Ib KontRASt-01 study, JDQ443 has shown initial evidence of clinical activity in *KRAS G12C*-mutated tumors[5,8]

Figure 1. JDQ443 binding mode and structure[5-7]



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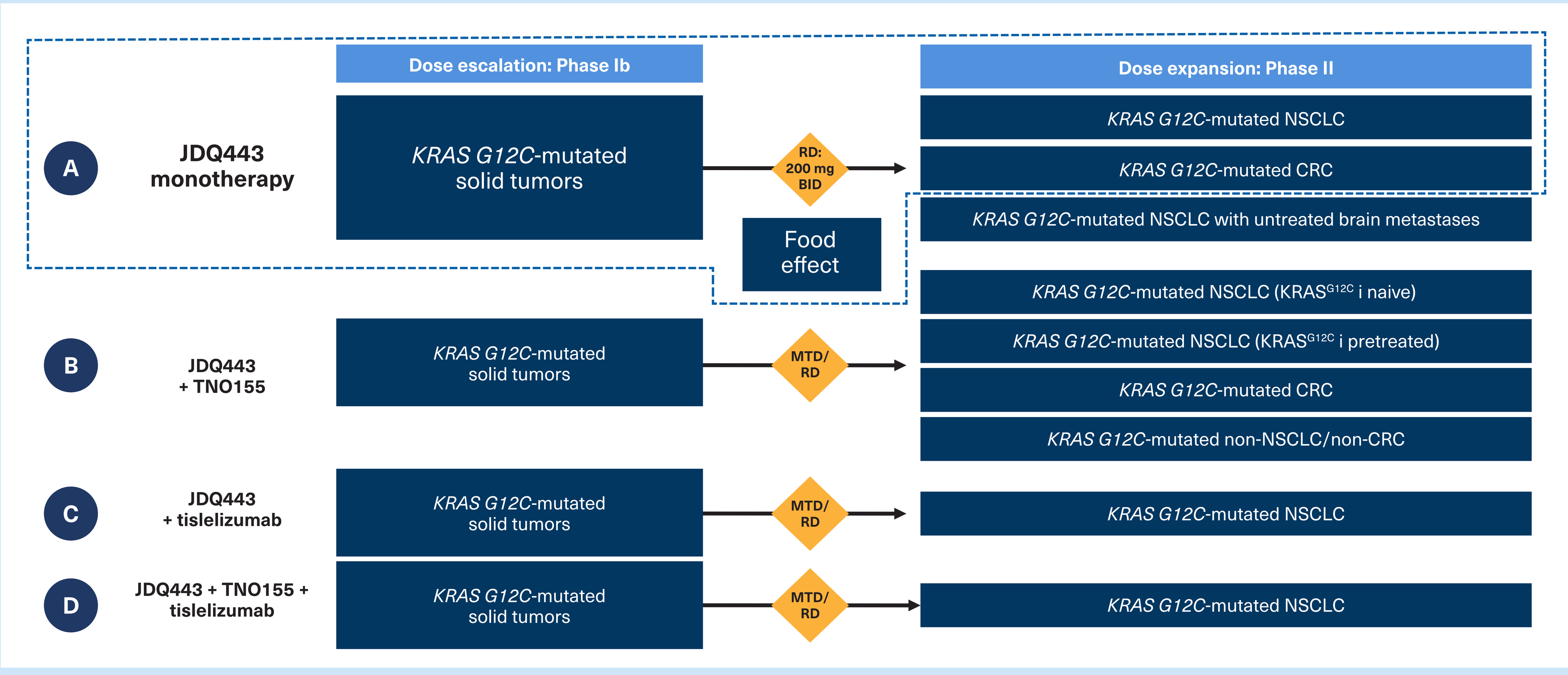
METHODS

- KontRASt-01 (NCT04699188) is a Phase Ib/II, open-label, multicenter, dose-escalation (DEs), and dose-expansion (DEx) trial of JDQ443 as a monotherapy or in combination with TNO155 (SHP2 inhibitor) and/or tislelizumab (anti–programmed death protein-1 monoclonal antibody) (**Figure 2**)

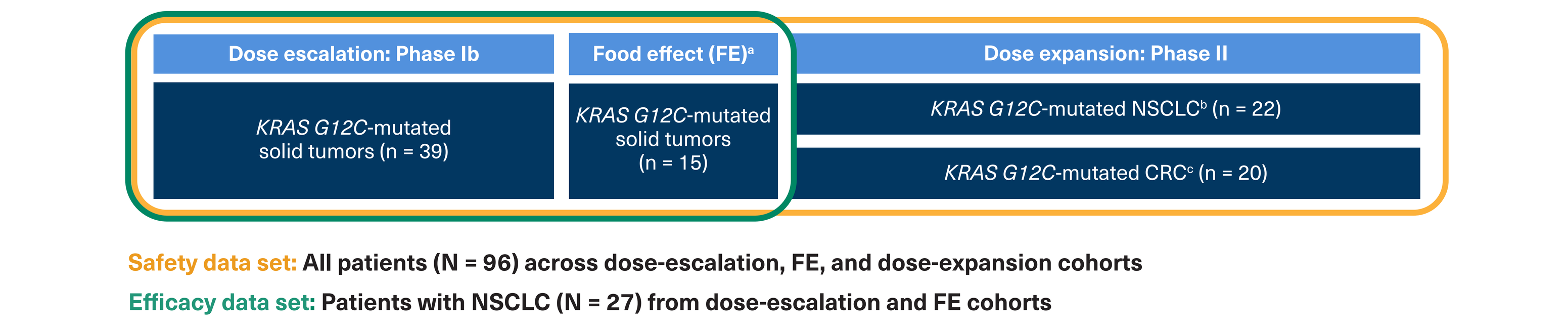
Figure 2. KontRASt-01: Overall study design



BID, twice daily; CRC, colorectal cancer; KRAS, Kirsten rat sarcoma viral oncogene homolog; KRAS[G12C] i, KRAS[G12C] inhibitor; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; RD, recommended dose for expansion.
Data presented are from a cutoff date of February 1, 2023. Presented data encompass study population indicated by blue dotted box.

- The monotherapy study population is described in **Figure 3**

Figure 3. JDQ443 monotherapy study population



CRC, colorectal cancer; KRAS, Kirsten rat sarcoma viral oncogene homolog; NSCLC, non-small cell lung cancer.
Data presented are from a cutoff date of February 1, 2023. Pre-planned analyses in the Phase II NSCLC expansion group will be the subject of future presentations.
[a]Patients in the FE cohort received treatment on an empty stomach, at least 1 hour before and 2 hours after a meal, from day 1 to day 7. Following a washout period with no treatment on day 8, patients commenced standard treatment cycles at the same dose and schedule, receiving JDQ443 with food. For dose escalation and dose expansion, JDQ443 was dosed with food at all time points. [b]All patients with NSCLC must have been previously treated with a platinum-based chemotherapy regimen and an immune checkpoint inhibitor, either in combination or in sequence, unless ineligible to receive such therapy. [c]Patients with CRC must have previously received standard-of-care therapy, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, unless ineligible to receive such therapy.

- The key objectives for DEs and DEx, as well as the key eligibility criteria, are shown in **Table 1**

Table 1. JDQ443 monotherapy study population

Key objectives for dose escalation	Key objectives for dose expansion
Primary: Assess the safety and tolerability of JDQ443 and identify the MTD and/or RD and regimen for future studies **Secondary:** Evaluate the antitumor activity and characterize the PK of JDQ443	**Primary:** Evaluate the antitumor activity of JDQ443 monotherapy **Secondary:** Assess the safety and tolerability and characterize the PK of JDQ443
Key eligibility criteria	
Patients with advanced, *KRAS G12C*-mutated solid tumors who have received standard-of-care therapy or who are intolerant of or ineligible for approved therapies; ECOG PS 0-1; no prior treatment with a KRAS[G12C] inhibitor	

ECOG, Eastern Cooperative Oncology Group; KRAS, Kirsten rat sarcoma viral oncogene homolog; MTD, maximum tolerated dose; PK, pharmacokinetics; PS, performance status; RD, recommended dose.

RESULTS

- Demographics and baseline characteristics are shown in **Table 2**

Table 2. Demographics and Baseline Characteristics

Dose selected for the Phase III studies: JDQ443 200 mg BID escalation + FE + expansion (n = 68)

	JDQ443 200 mg QD escalation (n = 10)	JDQ443 400 mg QD escalation (n = 11)	JDQ443 300 mg BID escalation (n = 7)	JDQ443 200 mg BID escalation + FE + expansion (n = 68)	All dose levels, pooled (N = 96)
Age, years					
Median	57.0	63.0	59.0	62.5	61.5
Range (min-max)	(30.0-73.0)	(50.0-76.0)	(27.0-72.0)	(26.0-83.0)	(26.0-83.0)
Sex, n (%)					
Female	5 (50.0)	7 (63.6)	5 (71.4)	33 (48.5)	50 (52.1)
Number of prior lines of antineoplastic therapy					
Median	3	3	3	2	2
Range (min-max)	(1-5)	(1-7)	(2-6)	(1-7)	(1-7)
History of prior ICI therapy, n (%)					
Yes	5 (50.0)	7 (63.5)	–	33 (48.5)	45 (46.9)
ECOG PS, n (%)					
0	2 (20.0)	5 (45.5)	5 (71.4)	26 (38.2)	38 (39.6)
1	8 (80.0)	6 (54.5)	2 (28.6)	42 (61.8)	58 (60.4)
History of CNS metastasis, n (%)					
Yes	1 (10.0)	2 (18.2)	–	8 (11.8)	11 (11.5)
No	9 (90.0)	8 (72.7)	7 (100.0)	59 (86.8)	83 (86.5)
Unknown	–	1 (9.1)	–	1 (1.5)	2 (2.1)
Indication, n (%)					
NSCLC	6 (60.0)	7 (63.6)	–	36 (52.9)	49 (51.0)
CRC	4 (40.0)	3 (27.3)	6 (85.7)	30 (44.1)	43 (44.8)
Other[a]	–	1 (9.1)	1 (14.3)	2 (3.0)	4 (4.2)

BID, twice daily; CNS, central nervous system; CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; FE, food effect; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; PS, performance status; QD, once daily.
Data presented with a cutoff date of February 1, 2023. Among patients with NSCLC, 89.8% (44/49) had a history of prior ICI therapy.
[a]Other indications included one each of: appendix cancer, bile duct cancer, ovarian cancer, and pancreatic cancer.

- JDQ443 200 mg twice daily (BID) maximizes exposure and enables sustained KRAS[G12C] target occupancy (**Figures 4** and **5**)
  - The exposure increase plateaued at 200 mg following single dose and at steady state, likely due to saturation of absorption
  - Half-life of ~7 hours
  - There was no significant accumulation or autoinduction following once-daily or BID dosing (**Figure 4**)
  - Greater than 95% of the population is predicted to achieve >70% average target occupancy with JDQ443 200 mg BID (**Figure 5**)

Figure 4. Steady-state plasma PK[a]

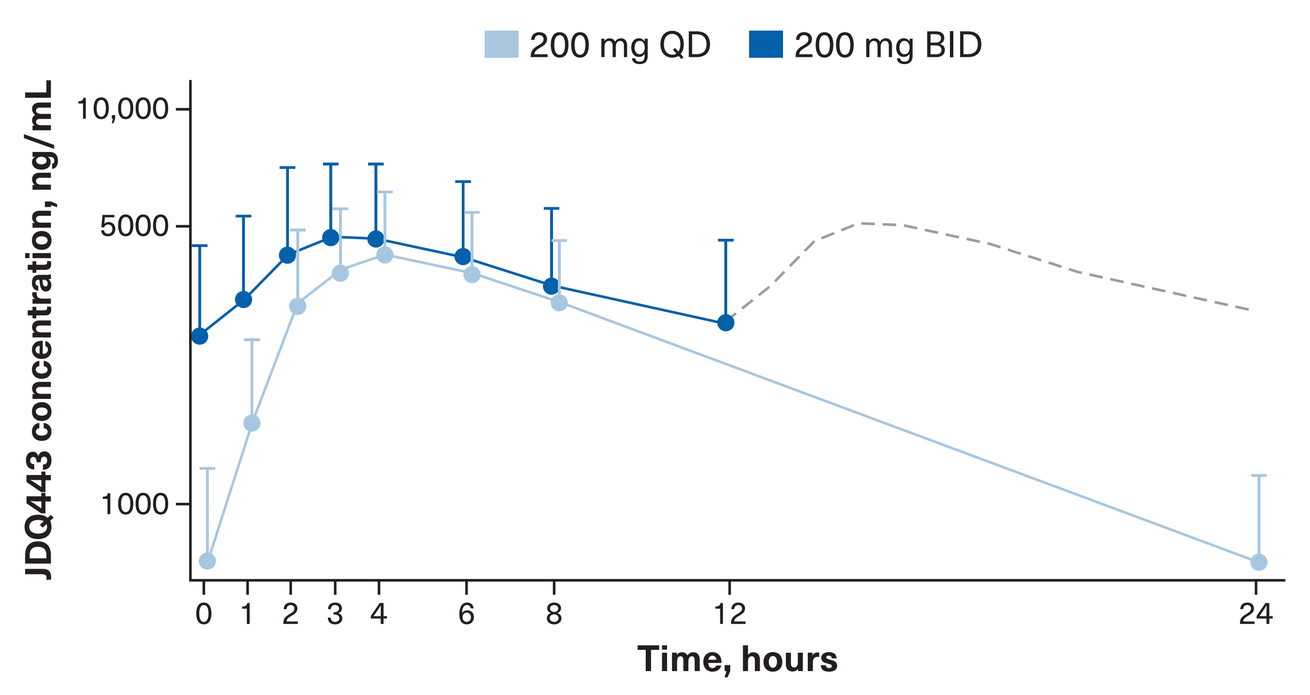
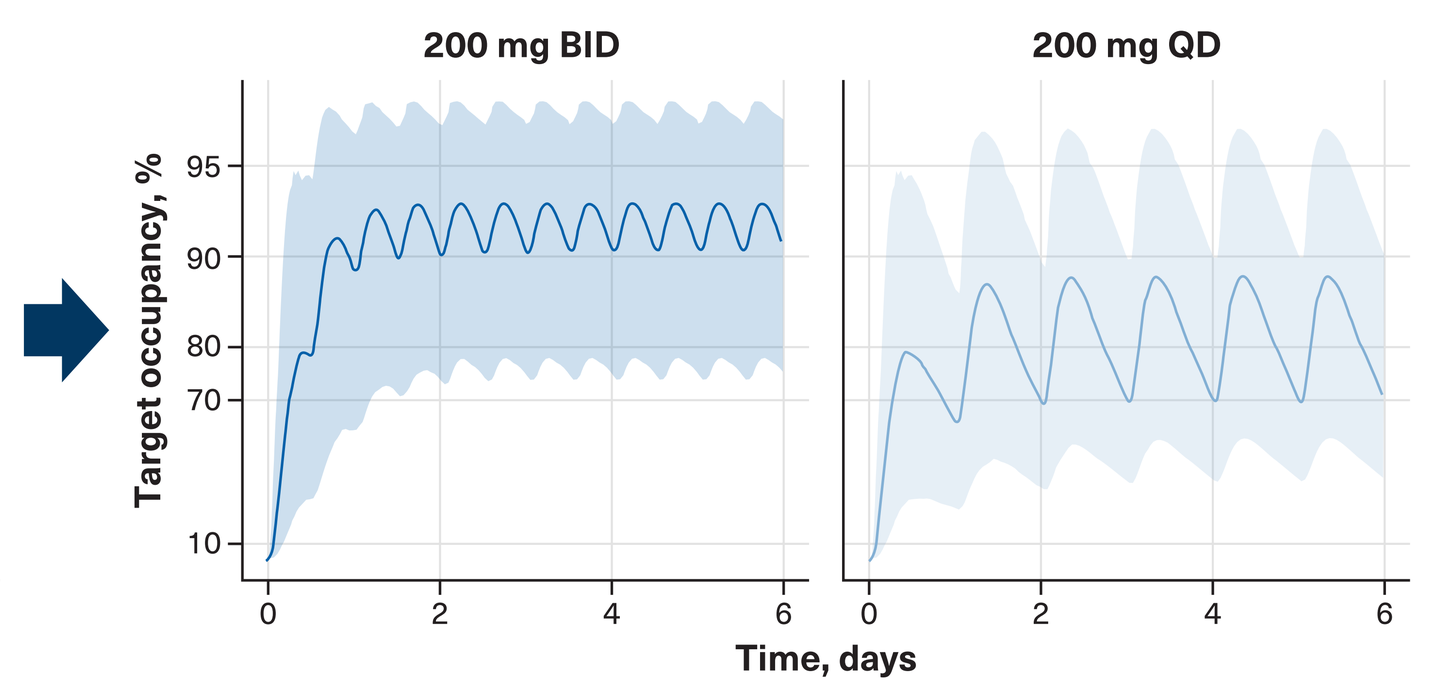


Figure 5. Predicted KRAS[G12C] target occupancy[b]



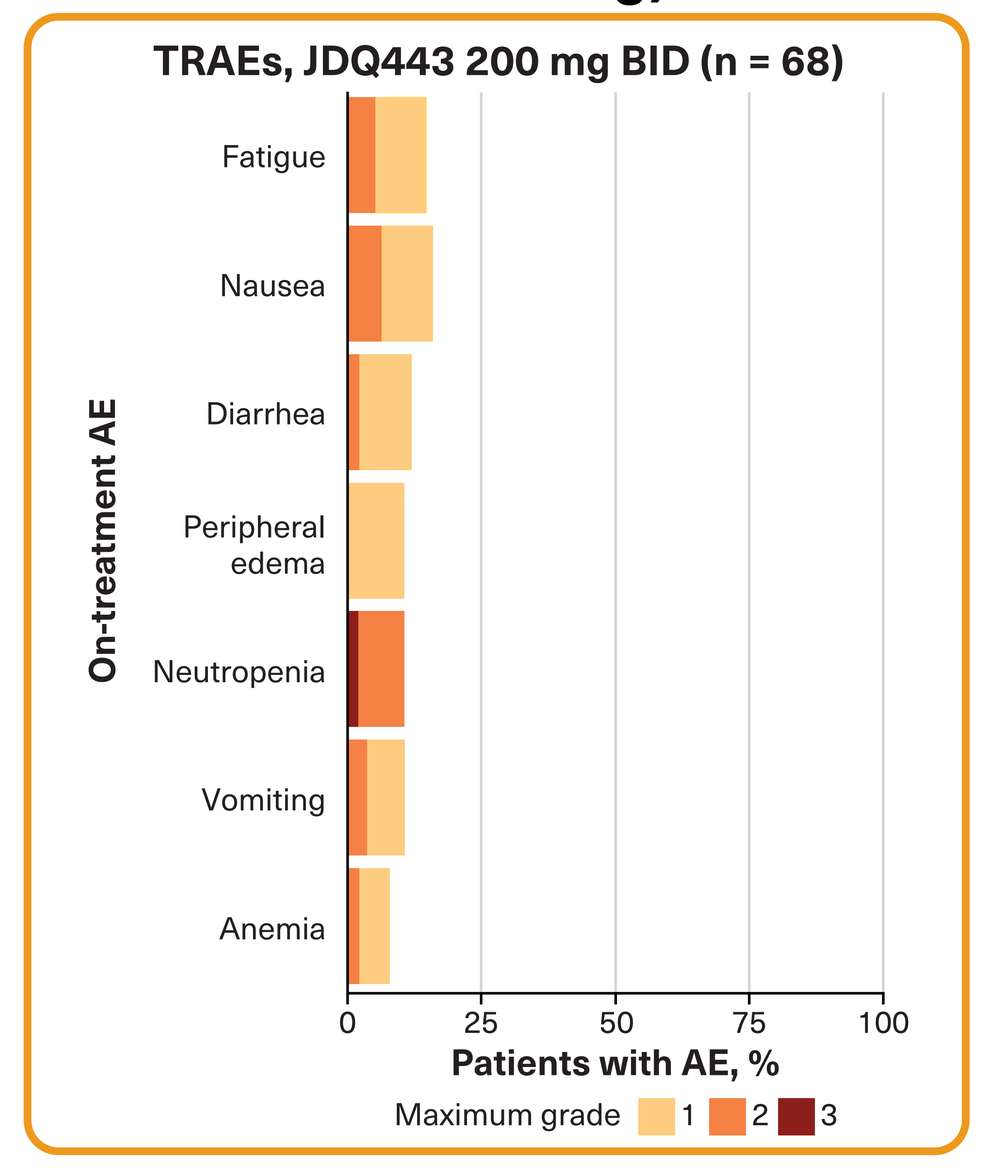
BID, twice daily; KRAS, Kirsten rat sarcoma viral oncogene homolog; PK, pharmacokinetics; QD, once daily.
Data presented with a cutoff date of January 23, 2023. Error bars indicate standard deviation for PK profiles at each time point. Target occupancy plot solid lines show median target occupancy and shaded areas show 5th to 95th percentile prediction intervals.
[a]For 200-mg BID continuous dosing, PK sampling is not performed during 12 to 24 hours. The dashed gray line represents the expected PK profile. [b]Assumptions: JDQ443 binding and target (KRAS) turnover rates are the same in mice and humans (~25-hour half-life for KRAS); only free drug can bind target. The >70% average target occupancy threshold results in maximal tumor shrinkage in preclinical models.

- Treatment-related adverse events (TRAEs) are reported in **Table 3** and **Figure 6**
  - TRAEs were low-frequency, low-grade events
  - There were no grade 4 or 5 TRAEs
  - No nausea/vomiting/diarrhea higher than grade 2

Table 3. Treatment-Related Adverse Events (≥10% of All Patients)

	JDQ443 200 mg QD escalation (n = 10)		JDQ443 400 mg QD escalation (n = 11)		JDQ443 300 mg BID escalation (n = 7)		JDQ443 200 mg BID escalation + FE + expansion (n = 68)		All dose levels, pooled (N = 96)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Patients with at least one event, n (%)	**8 (80.0)**	**2 (20.0)**	**8 (72.7)**	**1 (9.1)**	**6 (85.7)**	**5 (71.4)**	**51 (75.0)**	**4 (5.9)**	**73 (76.0)**	**12 (12.5)**
Fatigue	5 (50.0)	2 (20.0)	3 (27.3)	–	4 (57.1)	1 (14.3)	11 (16.2)	–	23 (24.0)	3 (3.1)
Nausea	3 (30.0)	–	1 (9.1)	–	–	–	12 (17.6)	–	16 (16.7)	–
Diarrhea	2 (20.0)	–	2 (18.2)	–	1 (14.3)	–	9 (13.2)	–	14 (14.6)	–
Peripheral edema	2 (20.0)	–	2 (18.2)	–	1 (14.3)	–	8 (11.8)	–	13 (13.5)	–
Neutropenia	–	–	1 (9.1)	–	2 (28.6)	1 (14.3)	8 (11.8)	2 (2.9)	11 (11.5)	3 (3.1)
Vomiting	2 (20.0)	–	–	–	–	–	8 (11.8)	–	10 (10.4)	–
Anemia	2 (20.0)	–	2 (18.2)	–	–	–	6 (8.8)	–	10 (10.4)	–

Figure 6. Treatment-related adverse events for patients who received JDQ 200 mg)



AE, adverse event; ALT, alanine aminotransferase; AST; aspartate aminotransferase; BID, twice daily; CTCAE, Common Terminology Criteria for Adverse Events; FE, food effect; QD, once daily; SAE, serious AE; TRAE, treatment-related AE.
Data presented with a cutoff date of February 1, 2023. All AEs were graded per CTCAE version 5.0. Two patients experienced treatment-related SAEs: grade 3 photosensitivity reaction and grade 2 rash erythematous in one patient; grade 3 bullous dermatitis in one patient; all occurred at 300 mg BID. Treatment was discontinued by three patients for treatment-related events: two patients due to elevated ALT and one patient due to nausea, diarrhea, and vomiting. Seven patients had dose reductions across the following groups: 200 mg QD (n = 2), 200 mg BID (n = 2), and 300 mg BID (n = 3). Two patients from the 200-mg BID group had dose reductions: one patient due to grade 3 ALT elevation and grade 3 AST elevation, and one patient due to grade 2 peripheral neuropathy.

- Overall, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations were low-frequency and short-duration events (**Figure 7** and **Table 4**)
- There was no association between ALT/AST elevation (grade ≥1) and JDQ443 exposure by exposure-response analysis

Figure 7. ALT/AST values over time represented by CTCAE grading, regardless of attribution

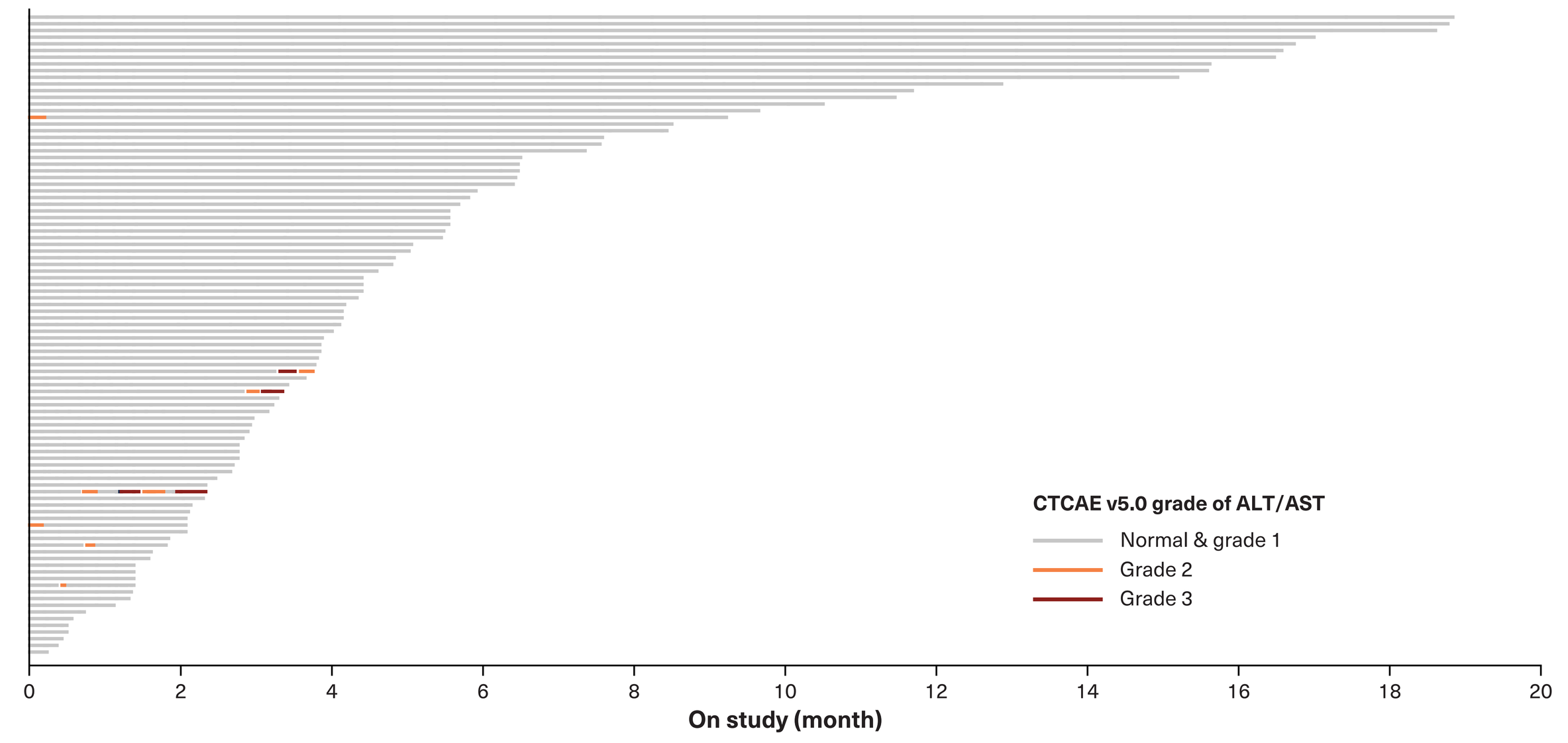


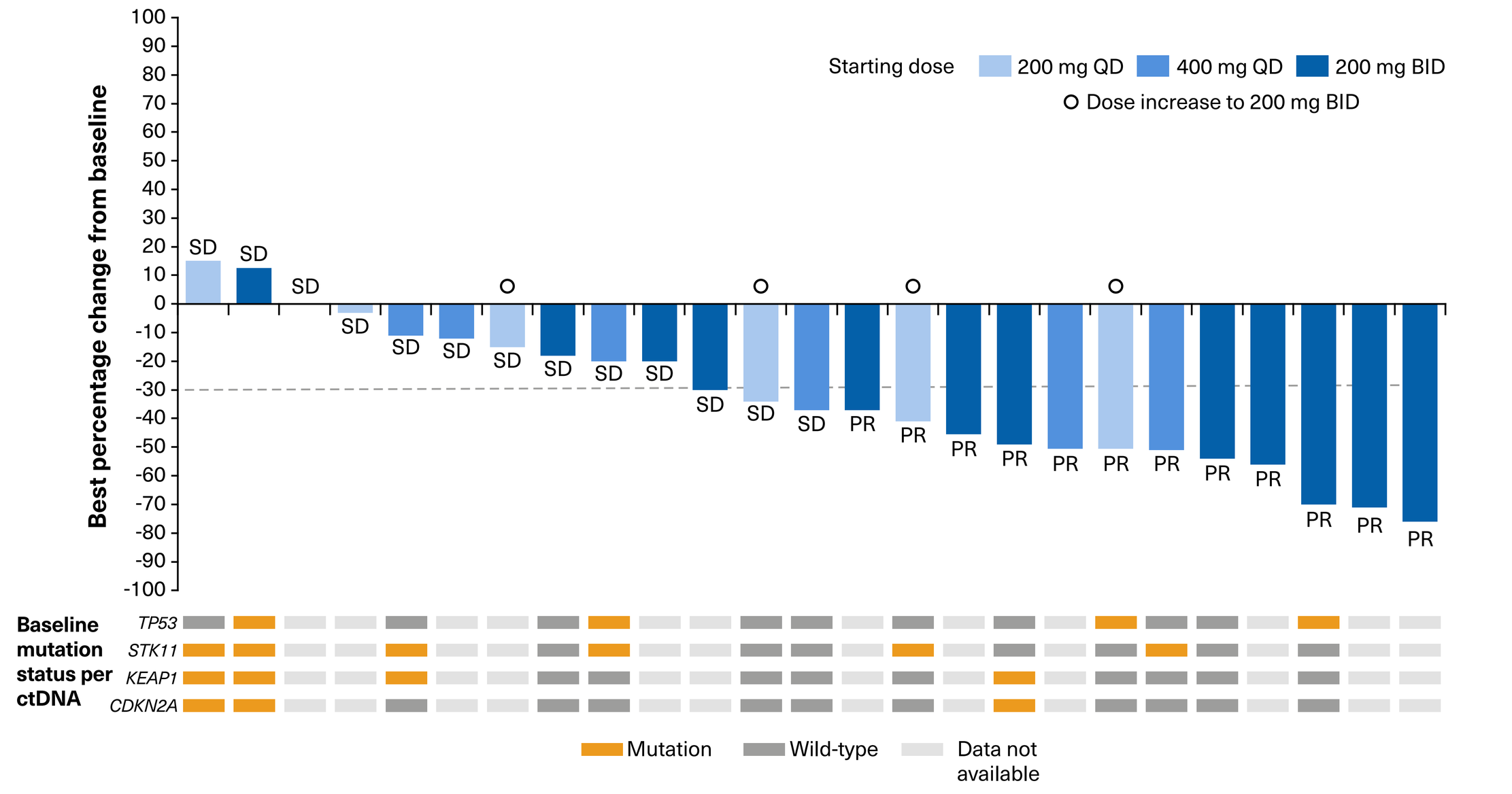
Table 4. Investigator-Reported Treatment-Related Adverse Events

	JDQ443 200 mg BID (n = 68)	JDQ443 All dose levels, pooled (N = 96)
Highest grade ALT elevation, n (%)		
Grade 1	2 (2.9)	3 (3.1)
Grade 2	–	1 (1.0)
Grade 3	2 (2.9)	2 (2.1)
All grades	4 (5.9)	6 (6.3)
Highest grade AST elevation, n (%)		
Grade 1	2 (2.9)	4 (4.2)
Grade 2	1 (1.5)	1 (1.0)
Grade 3	1 (1.5)	1 (1.0)
All grades	4 (5.9)	6 (6.3)

AE, adverse event; ALT, alanine aminotransferase; AST; aspartate aminotransferase; BID, twice daily; CTCAE v5.0, Common Terminology Criteria for Adverse Events version 5.0; FE, food effect.
Data presented with a cutoff date of February 1, 2023. Figure shows CTCAE v5-defined severity grades based on ALT/AST lab values, plotting highest grade ALT or AST over time for each patient (not by investigator AE report). Table shows investigator-reported treatment-related AEs. No grade 4 or 5 elevations were observed.

- Best overall response data are reported in **Figure 8**
  - Preliminary overall response rate (ORR): 57.1% (8/14) at recommended DEx of 200 mg BID

Figure 8. NSCLC: Best overall response

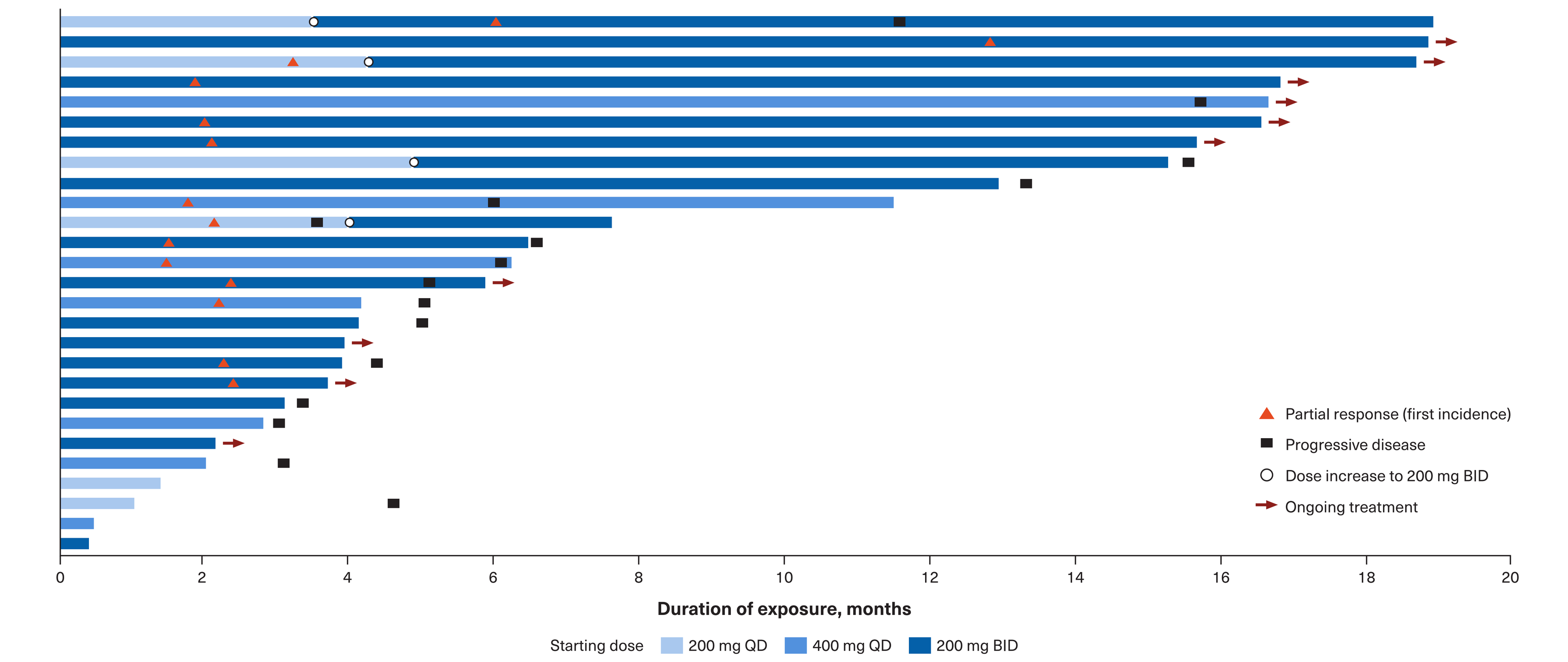


	JDQ443 200 mg BID (n = 14)	JDQ443 All dose levels, pooled (n = 27)
Confirmed ORR, %	57.1	44.4
DCR, %	92.9	92.6
BOR[a], n (%)		
PR	8 (57.1)	12 (44.4)
SD	5 (35.7)	13 (48.1)
PD	0	0
Unknown	1 (7.1)	2 (7.4)

BID, twice daily; ctDNA, circulating tumor DNA; DCR, disease control rate; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD, progressive disease; PR, partial response; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.
Data presented with a cutoff date of February 1, 2023. Waterfall plot: 25 (92.6%) patients with NSCLC with available change from baseline tumor assessments; data are plotted out of n = 27 patients with NSCLC who received JDQ443 single agent. Patients were enrolled in dose-escalation and food-effect cohorts.
[a]Best overall response per RECIST v1.1 based on investigator's assessment. Intrapatient dose escalation, per protocol, occurred in four patients from 200 mg QD to 200 mg BID. Mutation detection: plasma ctDNA at baseline; assay validated to 0.5% allele frequency. 95% CI for ORR: 28.9-82.3 for 200 mg BID; 25.5-64.7 for all dose levels.

- Duration of treatment is shown in **Figure 9**
  - Median duration of treatment was 4.9 months

Figure 9. NSCLC: Duration of treatment and onset of response



BID, twice daily; NSCLC, non-small cell lung cancer; QD, once daily; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.
Data presented with a cutoff date of February 1, 2023. Responses are investigator assessed per RECIST v1.1. Both confirmed and unconfirmed PRs are presented. Treatment beyond progression was allowed for patients with evidence of ongoing clinical benefit.

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