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Efficacy and Safety of Taletrectinib in Patients With ROS1+ Non-Small Cell Lung Cancer (NSCLC): Interim Analysis of Global TRUST-II Study

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Objectives

TRUST-II is evaluating the efficacy and safety of taletrectinib in patients with advanced or metastatic ROS1+ NSCLC and other solid tumors

Background

- Taletrectinib is a next-generation, CNS-active, ROS1 TKI with selectivity over TRKB[1]
  - Potent against ROS1 and acquired-resistance mutations, such as G2032R[1]
  - Clinical exposures at steady state sufficient to inhibit both ROS1 and ROS1^{G2032R}
- Taletrectinib previously demonstrated high overall and intracranial response rates, prolonged PFS, and activity against G2032R, and had a favorable safety profile in the regional TRUST-I study (NCT04395677)[2]
  - Based on these findings, taletrectinib was granted a breakthrough therapy designation by the FDA for treatment of adults with advanced or metastatic ROS1+ NSCLC who are ROS1 TKI treatment-naive or previously treated with crizotinib
- Here, we present the interim results from the global pivotal phase 2 trial, TRUST-II (NCT04919811), evaluating taletrectinib in patients with advanced ROS1+ NSCLC from North America, Europe, and Asia[1]

Abbreviations

AE, adverse event; AST, aspartate aminotransferase; ALT, alanine aminotransferase; C, crizotinib CI, confidence interval; CNS, central nervous system; CPK; creatinine phosphokinase; CT, chemotherapy; cORR, confirmed objective response rate; cCR, confirmed complete response; cPR, confirmed partial response; DCR, disease control rate; DoR, duration of response; E, entrectinib ECG; electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, intracranial; IQR, interquartile range; IRC, independent review committee; mDoR, median duration of response; mPFS, median progression-free survival; NR, not reached; NSCLC, non small cell lung cancer; OS, overall survival; PD, progressive disease; PFS, progression-free survival; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor; TRKB, tropomyosin receptor kinase B; TTR, time to response.

References

1. Nagasaka M, et al. *Future Oncol.* 2023;19(2):123-135.
2. Li W, et al. *J Thorac Oncol.* 2023;S47.

Acknowledgments

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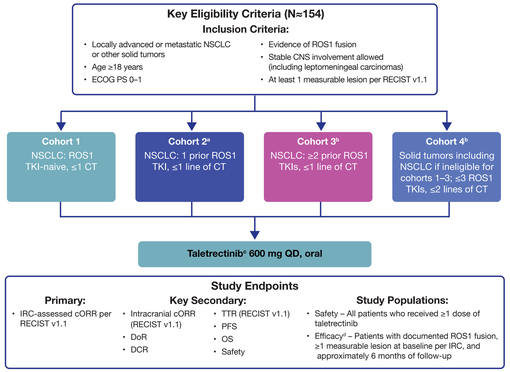
Methods

- TRUST-II (NCT04919811), a global phase 2, multicenter, open-label, single-arm study in patients with ROS1+ tumors, has 4 cohorts

TRUST II (NCT04919811) Study Design



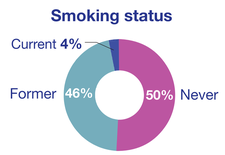
[a]Prior TKI use was limited to approved ROS1 TKIs (crizotinib or entrectinib). [b]Prior TKI use could include any ROS1 TKI regardless of approval status, per most recent protocol amendment 3.0. [c]Taletrectinib was administered in 21-day cycles. [d]For interim analysis only.

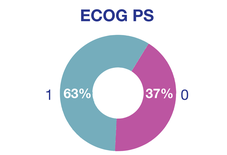
Results

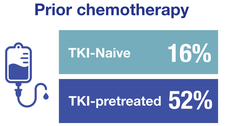
- Data cutoff date: July 12, 2023
- The efficacy population presented here includes patients from cohorts 1 and 2

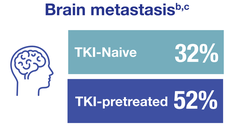
Patient Demographics and Baseline Characteristics (Efficacy Population)

46 patients enrolled in cohorts 1 and 2 with ~6 months of follow-up prior to July 12, 2023[a]	Median age: 58 y IQR: 52.8-67.0	21 (46%) of patients were female



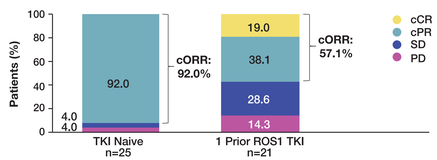






[a]The efficacy population consisted of 25 TKI-Naive patients in cohort 1 and 21 TKI-pretreated patients in cohort 2. [b]Brain metastasis status by IRC (RANO-BM). [c]25% (cohort 1) and 73% (cohort 2) of patients with baseline brain metastases had prior radiotherapy to the brain.

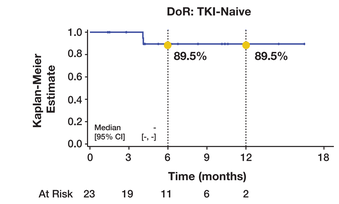
Responses by Cohort[a,b]

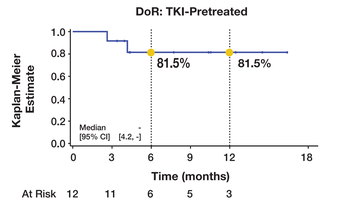


	TKI-Naive (n=25)	TKI-pretreated (n=21)
Median follow-up, months (95% CI)	8.1 (5.6, 11.7)	11.7 (5.5, 15.8)
Median PFS, months (95% CI)	NR (12.0, NR)	11.7 (4.0, NR)
12-month PFS rate, % (95% CI)	82.3 (59.2, 93.0)	42.6 (18.0, 65.5)

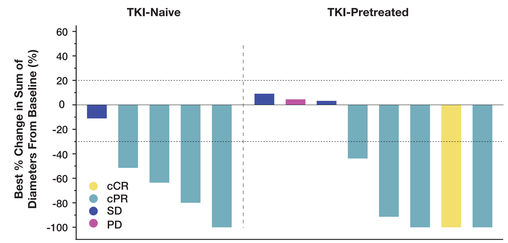
[a]Efficacy population. [b]Assessed by an independent review committee per RECIST v1.1.

- Duration of response was not mature in either cohort





Efficacy in Patients With Brain Metastases[a]



	TKI-Naive (n=5)	TKI-pretreated (n=8)
IC-cORR, % (n/N) [95% CI]	80.0 (4/5) [28.4, 99.5]	62.5 (5/8) [24.5, 91.5]

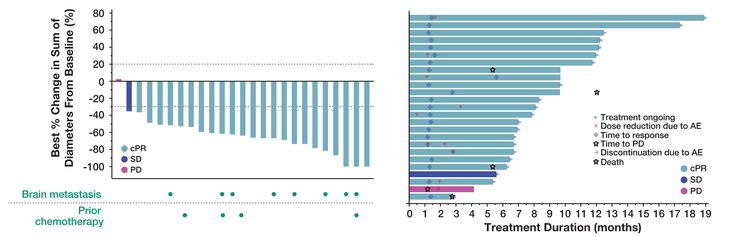
[a]Measurable lesions per RECIST v1.1.

Summary

- Interim analysis from the global pivotal TRUST-II study further establishes taletrectinib as a promising new option for patients with ROS1+ NSCLC
  - Tumor response was robust, durable, and consistent with TRUST-I
  - High overall response rates were observed in both TKI-naive (92%) and TKI-pretreated patients (57%)
  - Intracranial responses were robust in both TKI-naive (80%) and TKI-pretreated patients (63%)
- Taletrectinib demonstrated a favorable safety profile in ROS1 TKI-naive and TKI-pretreated NSCLC patients
  - TEAEs were mostly grade 1–2; incidence of dizziness was low (13%)
  - Low incidence of treatment discontinuations due to TEAEs
  - No treatment-related deaths
- Enrollment in this global phase 2 trial (NCT04919811) of taletrectinib is currently ongoing

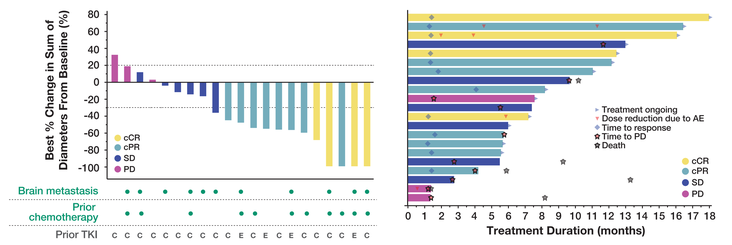
Efficacy in ROS1 TKI-Naive Patients (TKI-Naive; n=25)

- cORR: 92.0% (95% CI: 74.0, 99.0)



Efficacy in ROS1 TKI-Pretreated Patients (TKI-pretreated; n=21)

- cORR: 57.1% (95% CI: 34.0, 78.2)
- 17 patients (81%) in Cohort 2 received crizotinib (C); 4 (19%) received entrectinib (E)



Safety (Safety Population, n=107)[a]

- Median duration of exposure was 4.9 months (range: 0.09–18.9)
- Most common TEAEs: increased ALT (64%) and AST (63%), diarrhea (43%), and nausea (43%)
- Most TEAEs were grade 1–2
- 12% of patients had serious AEs
- Neurological TEAEs were low, majority were grade 1–2
  - 13% of patients experienced dizziness; most were grade 1
- TEAEs led to dose reduction in 34% of patients, the most common was increased liver enzymes (23%)
- 2% of patients had a TEAE leading to treatment discontinuation
- No taletrectinib-related deaths were reported

Patients With TEAEs (≥15%): Taletrectinib (Safety Population; n=107)[a]

TEAE, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All Grade
ALT increased	37 (34.6)	14 (13.1)	17 (15.9)	0	0	68 (63.6)
AST increased	40 (37.4)	23 (21.5)	4 (3.7)	0	0	67 (62.6)
Diarrhea	37 (34.6)	8 (7.5)	1 (0.9)	0	0	46 (43.0)
Nausea	32 (29.9)	11 (10.3)	3 (2.8)	0	0	46 (43.0)
Vomiting	23 (21.5)	7 (6.5)	1 (0.9)	0	0	31 (29.0)
Dysgeusia	13 (12.1)	7 (6.5)	0	0	0	20 (18.7)
Anemia	11 (10.3)	4 (3.7)	3 (2.8)	0	0	18 (16.8)
Constipation	15 (14.0)	3 (2.8)	0	0	0	18 (16.8)
Blood CPK increased	10 (9.3)	2 (1.9)	4 (3.7)	0	0	16 (15.0)

[a]Worst grade per patient is reported.

Supplemental materials

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Table S1. Patient Demographics and Baseline Characteristics (Efficacy Population)

Key Demographics	TKI-Naive (n=25) (%)	TKI-Pretreated (n=21) (%)
Age, median (range), y	60.0 (39–77)	55.0 (38–77)
Female, n (%)	11 (44.0)	10 (47.6)
Western/Asian region, n (%)	6 (24.0)/19 (76.0)	6 (28.6)/15 (71.4)
ECOG PS 0/1, n (%)	11 (44.0)/14 (56.0)	6 (28.6)/15 (71.4)
Prior chemotherapy, n (%)	4 (16.0)	11 (52.4)
Prior crizotinib/entrectinib, n (%)	0	7 (80.9)/4 (19.0)
Never/former/current smoker, n (%)	11 (44.0)/13 (52.0)/1 (4.0)	12 (57.1)/8 (38.1)/1 (4.8)
Brain metastasis, n (%)	8 (32.0)	11 (52.4)
Previously treated with radiotherapy, n (%)	2 (25.0)	8 (72.3)
Previously treated with stereotactic radiosurgery, n (%)	2 (25.0)	7 (63.6)
Previously treated with whole brain radiotherapy, n (%)	0	1 (9.1)

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Table S2. Taletrectinib Efficacy in ROS1^{+} NSCLC

Responses	TKI-Naïve (n=25) (%)	TKI-Pretreated (n=21) (%)
$cORR_{IRC}$, % (95% CI)[a]	92.0 (74.0, 99.0)	57.1 (34.0, 78.2)
DCR, % (95% CI)[a]	96.0 (79.7, 99.9)	85.7 (63.7, 97.0)
Median TTR, months (95% CI)	1.3 (1.3, 1.4)	1.4 (1.2, 1.6)

[a]Confidence intervals were calculated using the Clopper–Pearson method.

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Table S3. Patients with TEAEs (≥15%): Taletrectinib (Pooled Safety Population; n=355)[a]

TEAE, n (%)	Patients (N=355)	
	Any Grade n (%)	Grade ≥3 n (%)
Overall	353 (99.4)	179 (50.4)
AST increased	229 (64.5)	23 (6.5)
ALT increased	212 (59.7)	32 (9.0)
Diarrhea	208 (58.6)	11 (3.1)
Nausea	157 (44.2)	5 (1.4)
Vomiting	155 (43.7)	4 (1.1)
Anemia	110 (31.0)	10 (2.8)
Dizziness	68 (19.2)	1 (0.3)
Constipation	59 (16.6)	1 (0.3)
Decreased appetite	57 (16.1)	1 (0.3)
Blood creatinine increased	57 (16.1)	0
Dysgeusia	56 (15.8)	0
Neutrophil count decreased	56 (15.8)	17 (4.8)
WBC count decreased	55 (15.5)	5 (1.4)
Blood bilirubin increased	54 (15.2)	4 (1.1)

- TEAEs led to dose reduction in 22% of patients
- TEAEs led to dose discontinuation in 5.4% of patients

[a]Pooled analysis of safety data from 6 studies in patients treated with at least one dose of taletrectinib.

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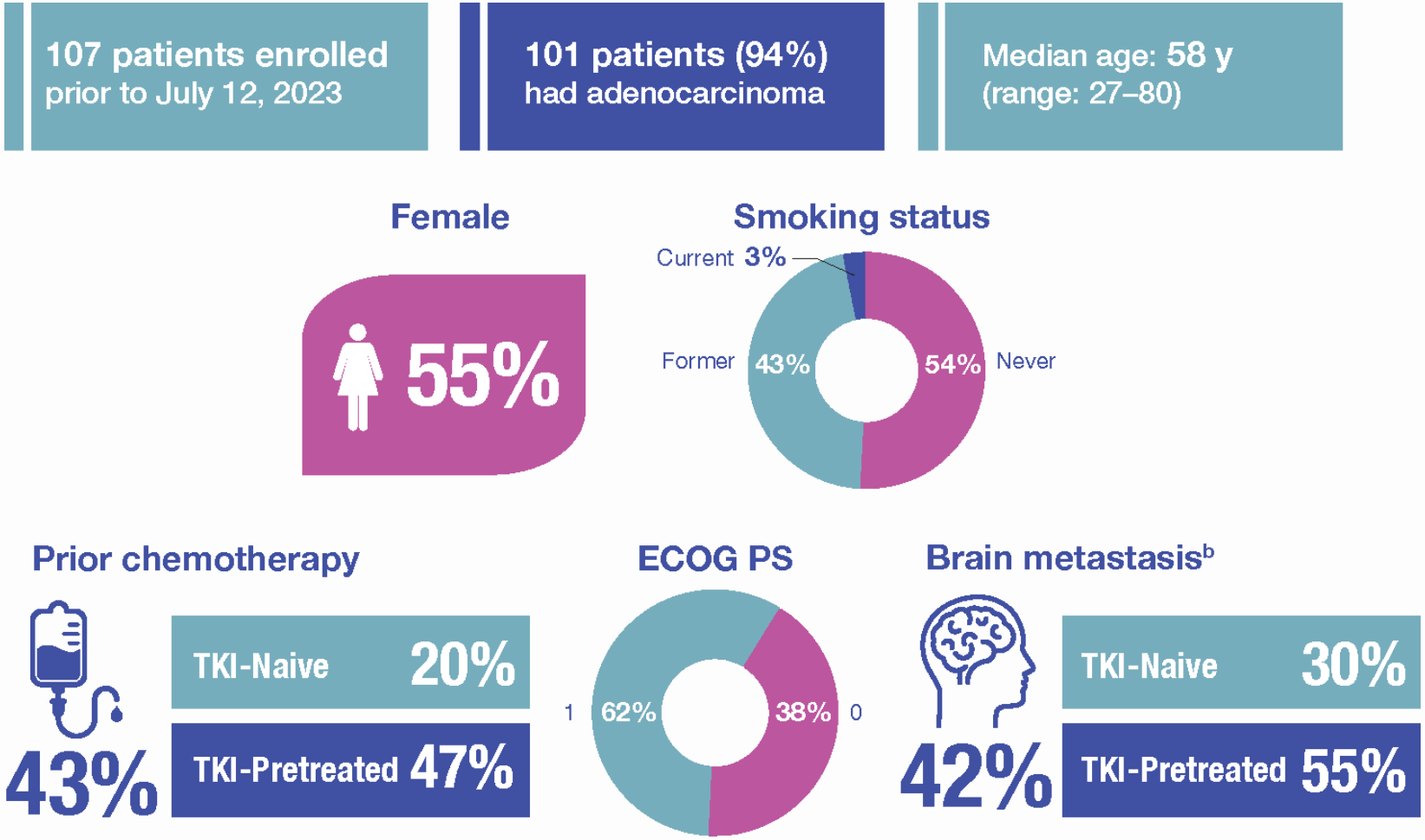
Fig S1: Patient Demographics and Baseline Characteristics[a] (Safety Population)



[a]The safety population included all patients who received ≥1 dose of taletrectinib in cohort 1 (n=44), cohort 2 (n=38), cohort 3 (n=22), and cohort 4 (n=3).
[b]Brain metastasis status by IRC (RANO-BM).

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Figure S2. Patient Responses Over Time

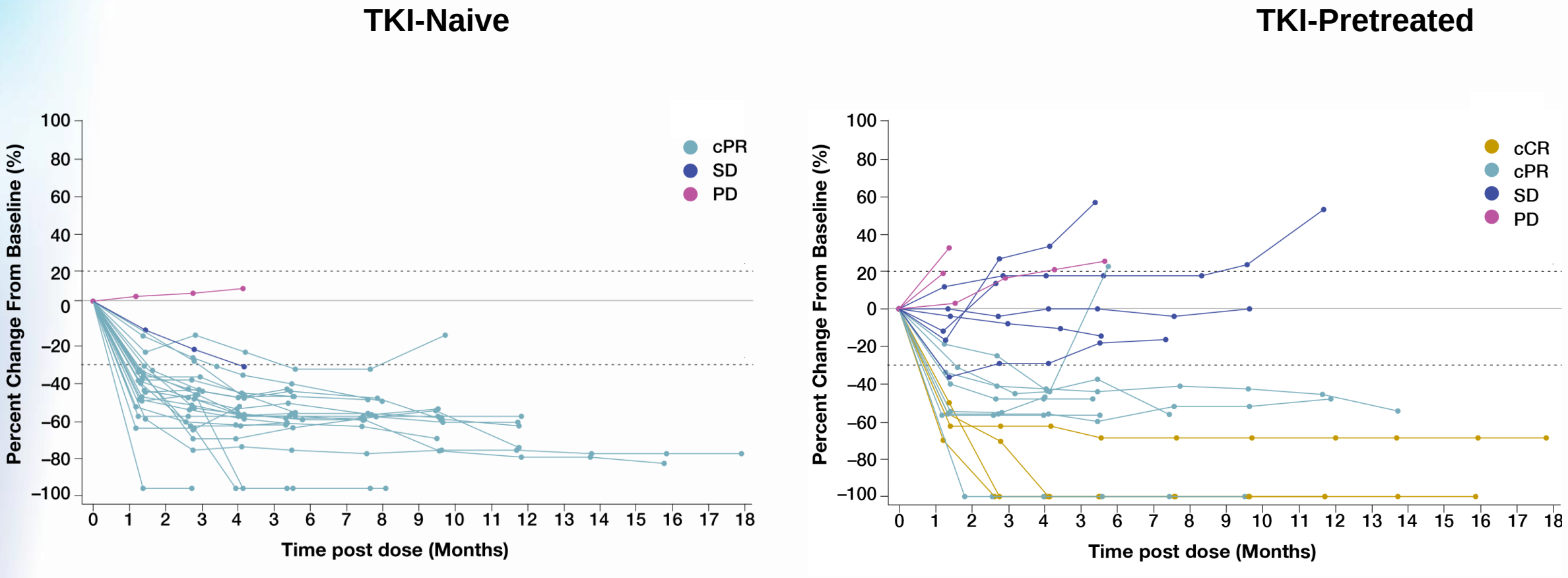

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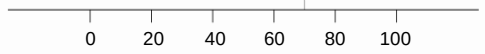
Figure S3: Best Overall Response by Subgroup

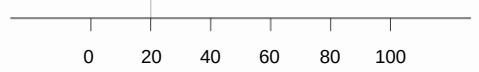
TKI-Naive

Subgroup	Number of Responders/Total Number of Patients	ORR (95% CI)
Overall	23/25	92.0 (73.97–99.02)
Age		
<65 Years	16/16	100.0 (79.41–100.00)
≥65 Years	7/9	77.8 (39.99–97.19)
Gender		
Male	12/14	85.7 (57.19–98.22)
Female	11/11	100.0 (71.51–100.00)
ECOG PS		
0	11/11	100.0 (71.51–100.00)
1	12/14	85.7 (57.19–98.22)
Brain Metastasis at Baseline by IRC (RANO-BM)		
Yes	8/8	100.0 (63.06–100.00)
No	15/17	88.2 (63.56–98.54)
Prior chemotherapy		
With prior chemotherapy	4/4	100.0 (39.76–100.00)
Without prior chemotherapy	19/21	90.5 (69.62–98.83)
Lines of Prior Anti-cancer Therapy		
0	19/21	90.5 (69.62–98.83)
1-2	3/3	100.0 (29.24–100.00)
≥3	1/1	100.0 (2.50–100.00)
Region		
Western	5/6	83.3 (35.88–99.58)
Asian	18/19	94.7 (73.97–99.87)
Smoking Status		
Smoker	12/14	85.7 (57.19–98.22)
Non-Smoker	11/11	100.0 (71.51–100.00)



TKI-Pretreated

Subgroup	Number of Responders/Total Number of Patients	ORR (95% CI)
Overall	12/21	57.1 (34.02–78.18)
Age		
<65 Years	8/16	50.0 (24.65–75.35)
≥65 Years	4/5	80.0 (28.36–99.49)
Gender		
Male	7/11	63.6 (30.79–89.07)
Female	5/10	50.0 (18.71–81.29)
ECOG PS		
0	5/6	83.3 (35.88–99.58)
1	7/15	46.7 (21.27–73.41)
Brain Metastasis at Baseline by IRC (RANO-BM)		
Yes	5/11	45.5 (16.75–76.62)
No	7/10	70.0 (34.75–93.33)
Prior chemotherapy		
With prior chemotherapy	8/11	72.7 (39.03–93.98)
Without prior chemotherapy	4/10	40.0 (12.16–73.76)
Lines of Prior Anti-cancer Therapy		
0	0	
1-2	7/16	43.8 (19.75–70.12)
≥3	5/5	100.0 (47.82–100.00)
Region		
Western	4/6	66.7 (22.28–95.67)
Asian	8/15	53.3 (26.59–78.73)
Smoking Status		
Smoker	5/9	55.6 (21.20–86.30)
Non-Smoker	7/12	58.3 (27.67–84.83)



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