Other Oncogene-Driven Cancers

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Discussion Outline

1. ***MET exon 14 – Resistance and Novel Therapies***

   OA21.04 – Amivantamab in Patients With Advanced NSCLC and MET Exon 14 Skipping Mutation: Results From the CHRYSALIS Study

2. ***KRAS G12C – TKI Updates and Beyond***

   MA06.04 – KRYSTAL-1: Two-Year Follow-Up of Adagrasib (MRTX849) Monotherapy in Patients With Advanced/Metastatic KRAS^{G12C}-Mutated NSCLC

   MA06.05 – CodeBreak 101: Safety and Efficacy of Sotorasib with Carboplatin and Pemetrexed in KRAS G12C-Mutated Advanced NSCLC

   MA06.03 – KontRASt-01: Preliminary safety and efficacy of JDQ443 + TNO155 in patients with advanced, KRAS G12C-mutated solid tumors

3. ***HER2 – Optimal Dosing of Trsastuzumab Deruxtecan***

   MA13.10 – Trastuzumab Deruxtecan in Patients With *HER2*-Mutant Metastatic Non-Small Cell Lung Cancer: Primary Results of DESTINY-Lung02

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Amivantamab in Patients With Advanced NSCLC and *MET* Exon 14 Skipping Mutation: Results From the CHRYSALIS Study

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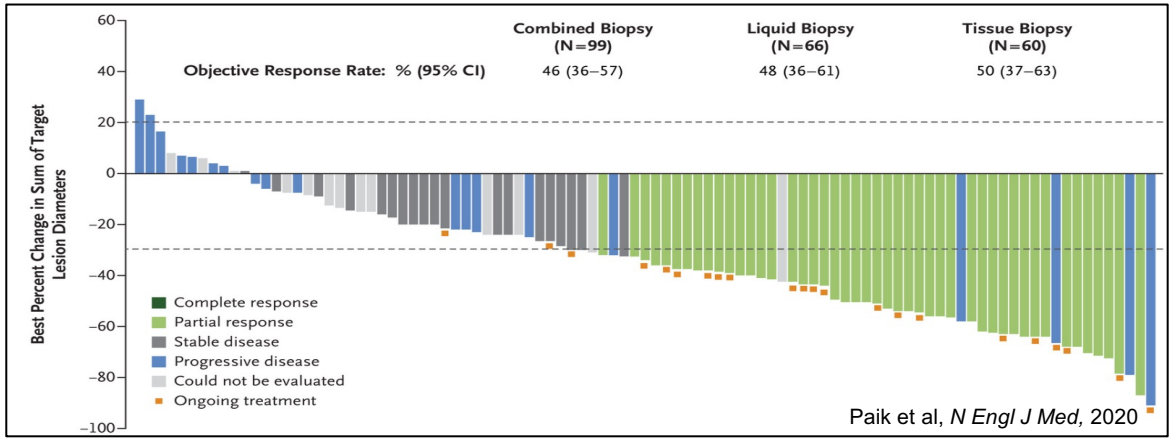
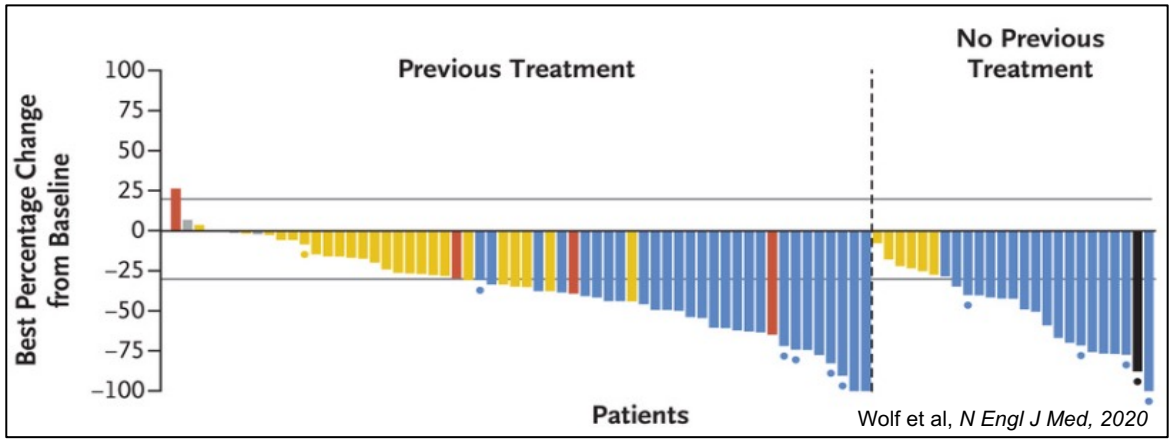
Targeted Therapy Landscape for *MET* exon 14 Skipping Mutations



Paik et al, *N Engl J Med*, 2020

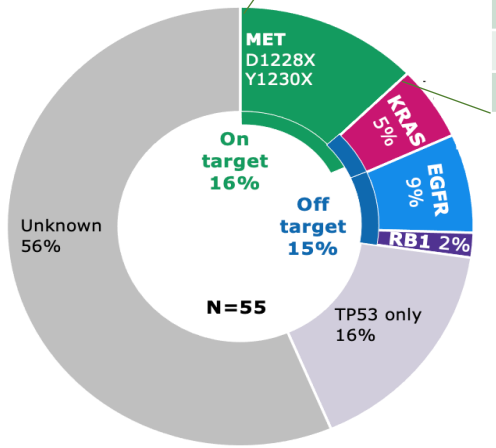
Tepotinib
ORR 57%
mPFS 12.6 mos



Wolf et al, *N Engl J Med*, 2020

Capmatinib
ORR 68%
mPFS 12.4 mos

Resistance



MET resistance mutations	BOR	PFS, months
D1228N	PR	13.9
D1228N	PR	11.2
D1228G	PR	10.6
D1228H	PR	8.3
Y1230C	PR	6.9
Y1230C	PR	6.9
Y1230H	PR	5.7
D1228H/Y, Y1230C/H	PD	2.7
D1228Y, Y1230H	NE	2.7

Le et al, WCLC Abstract OA21.06, 2023

Leighl et al, WCLC Abstract OA21.04, 2023

Study Schema – CHRYSALIS

Dose-escalation phase

RP2D was identified:
Amivantamab
1050 mg IV
(1400 mg if ≥80 kg)

Dose-expansion cohorts

- **Cohort A:** Post–any EGFR TKI (T790M+, C797S+)
- **Cohort B:** Post–any EGFR TKI (T790M–, C797S–)
- **Cohort C:** Post-osimertinib (C797S+)
- **Cohort D:** *EGFR* Ex20ins[a]
- **Cohort MET-1:** Post–any EGFR TKI (*MET* amplified)
- **Cohort MET-2:** *MET*ex14[b]
- **Cohorts WT:** *EGFR* wild-type status

Endpoints

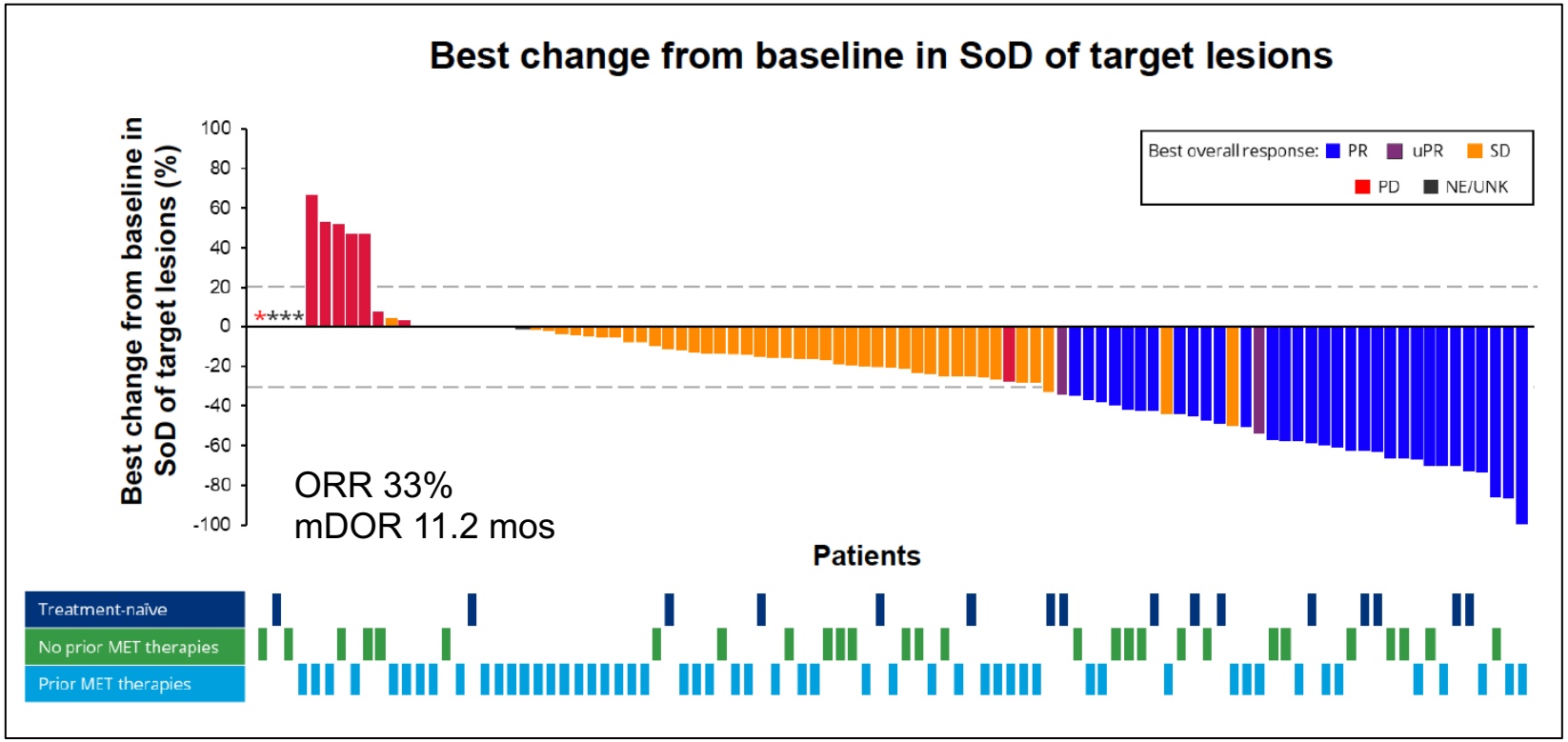
- Objective response rate (primary)
- Duration of response
- Clinical benefit rate[c]
- Progression-free survival
- Overall survival
- Adverse events

Focus of this presentation

Baseline Demographics

Characteristic, n (%)	Treatment-naïve (n = 16)	Previously treated		Total (n = 97)
		No prior MET therapies (n = 28)	Prior MET therapies (n = 53)	
Median age, years (range)	70 (57–86)	69 (49–83)	71 (43–88)	70 (43–88)
Female / male	8 (50) / 8 (50)	15 (54) / 13 (46)	29 (55) / 24 (45)	52 (54) / 45 (46)
Race				
Asian	10 (63)	16 (57)	21 (40)	47 (49)
White	6 (38)	9 (32)	23 (43)	38 (39)
Black	0	0	2 (4)	2 (2)
Not reported	0	3 (11)	7 (13)	10 (10)
History of brain metastases	1 (6)	4 (14)	9 (17)	14 (14)
ECOG PS				
0	7 (44)	4 (14)	8 (15)	19 (20)
1	9 (56)	23 (82)	45 (85)	77 (79)
2	0	1 (4)	0	1 (1)
History of smoking: yes / no	10 (63) / 6 (38)	14 (50) / 14 (50)	26 (49) / 27 (51)	50 (52) / 47 (48)
Median number of prior lines (range)	0	1 (1–4)	3 (1–10)	2 (0–10)

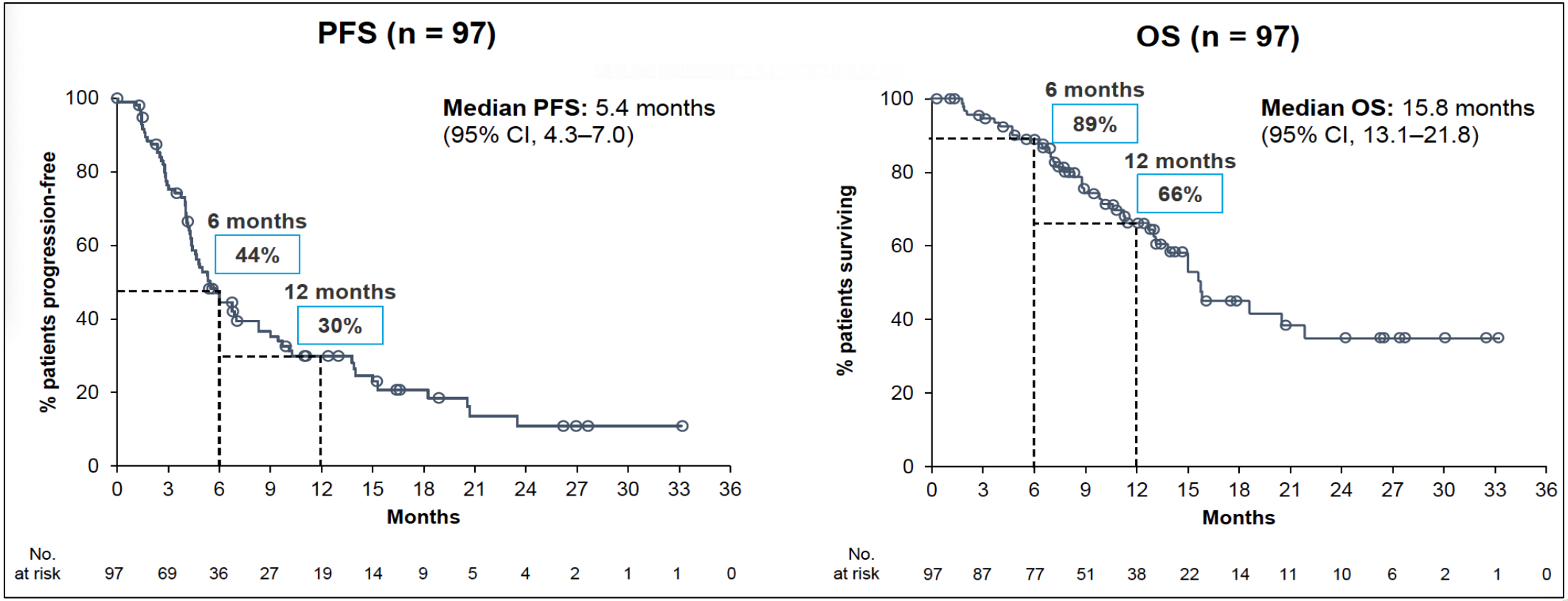
Efficacy of Amivantamab



	Treatment-naïve	No prior MET therapy	Prior MET therapy
ORR	50%	46%	21%
CBR	88%	64%	66%

ORR = objective response rate; CBR = clinical benefit rate

Progression-Free and Overall Survival



Overcoming Secondary MET Resistance

	Drug name	Inhibitor type	RESISTANCE MUTATION ACTIVITY			
			Solvent-Front	Activation-Loop	Beta-9 strand	Hydrophobic-core
Target active state of MET	**Crizotinib**	DFG-Din	G1163R	Y1230C/H/N/S; D1231Y	D1228N/H/E	L1995V
	Tepotinib	DFG-Din	G1163E	Y1230X	D1228X	L1995V
	Capmatinib	DFG-Din	Active on cell lines	Y1230H	D1228N/H	L1995V
	Savolitinib	DFG-Din	Active on cell lines	Y1230S	D1228N/V	L1995V
Target inactive state of MET	**Cabozantinib**	DFG-Dout	Variably active on cell lines	Known to be active	D1228Y/A/N	L1195V; F1200L
	Merestinib	DFG-Dout	Active on cell lines	Known to be active	D1228Y	F1200I
	Glesatinib	DFG-Dout	H1094Y	Known to be active	D1228Y/A	L1195V

- Amivantamab is active *MET* exon 14 skipping-positive NSCLC, although response rates are higher in those without prior MET-directed therapy (ORR 46 vs 21%).
- Among TKI therapies targeting *MET*, there are type I and type II inhibitors (see table) that have variable activity against different resistance mutations.
- Further understanding of amivantamab's activity against *MET* resistance mutations will help identify the best sequence of use for different *MET*-directed targeted therapies.

Fujino et al, *J Thorac Oncol,* 2019
Drilon et al, WCLC Abstract OA21.07, 2023
Leighl et al, WCLC Abstract OA21.04, 2023

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KRYSTAL-1: Two-Year Follow-Up of Adagrasib (MRTX849) Monotherapy in Patients With Advanced/Metastatic KRAS^{G12C}-Mutated NSCLC

Shirish M. Gadgeel[1], Pasi A. Jänne[2], Alexander I. Spira[3], Sai-Hong Ignatius Ou[4], Rebecca S. Heist[5], Jose M. Pacheco[6], Melissa L. Johnson[7], Joshua K. Sabari[8], Konstantinos Leventakos[9], Joshua A. Mason[10], Karen Velastegui[10], Xiaohong Yan[10], Richard Chao[10], Gregory J. Riely[11]

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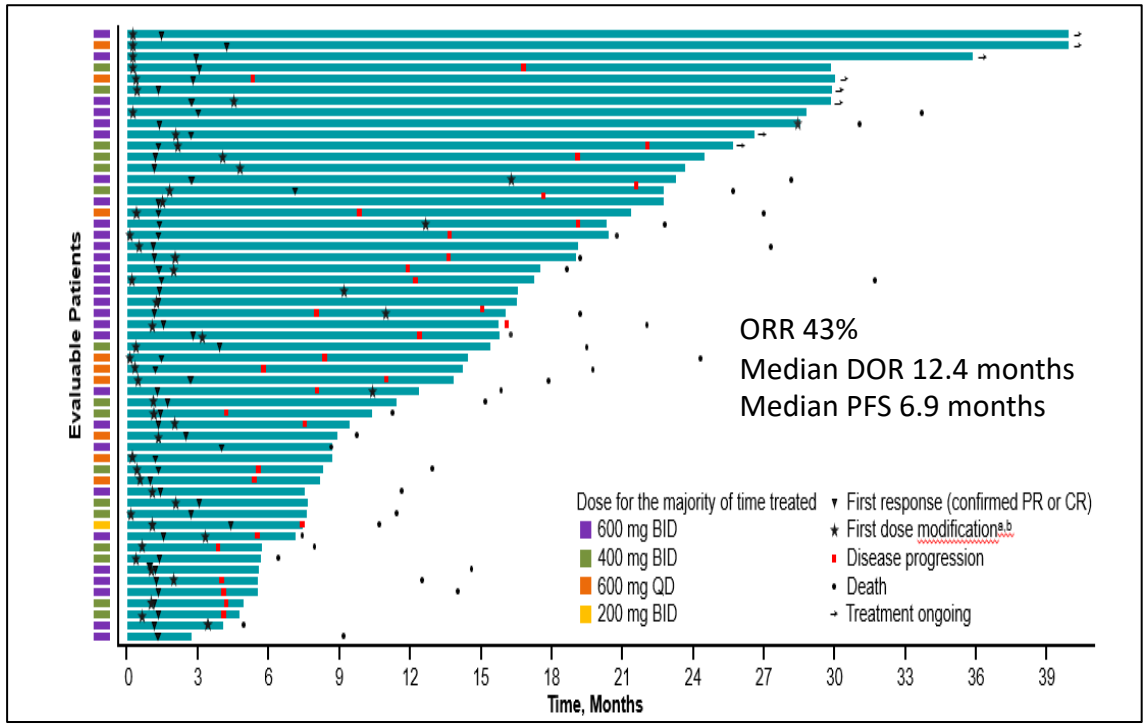
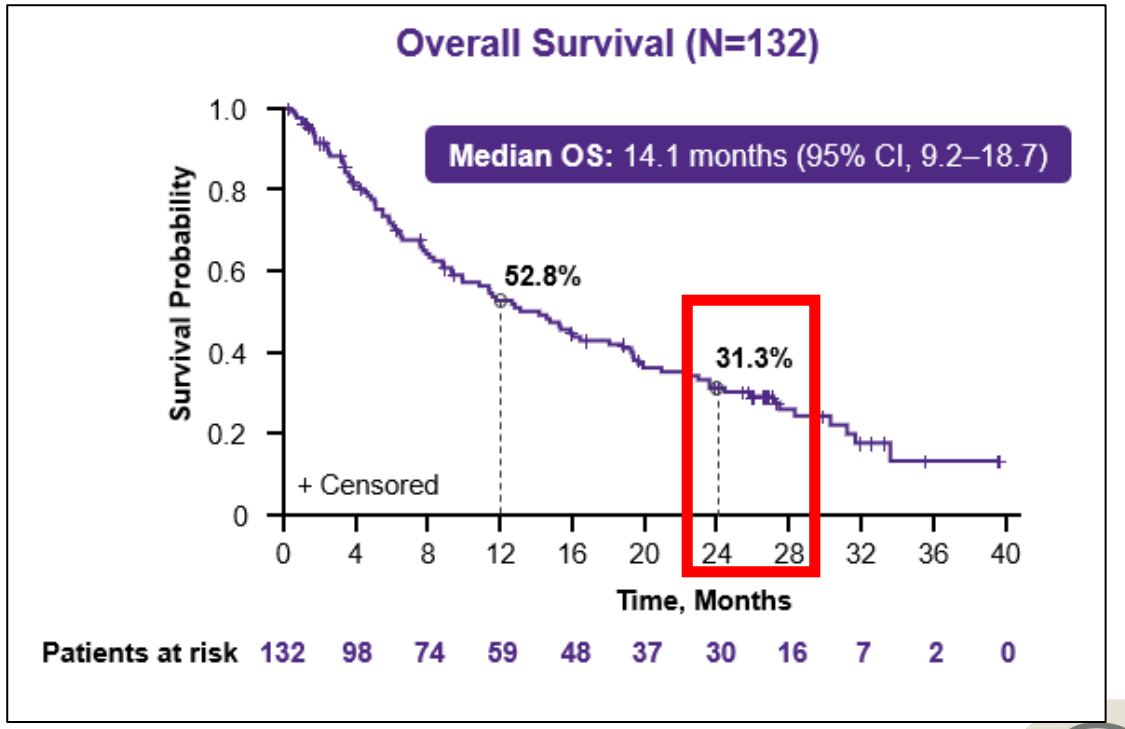
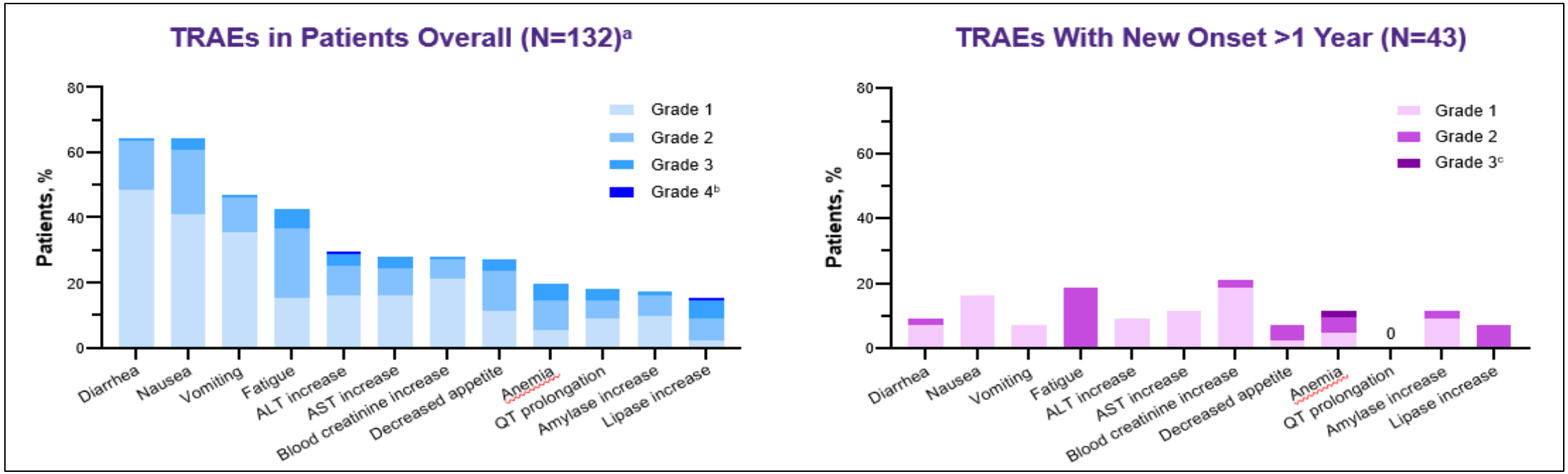
Updated Efficacy and Survival With Adagrasib





Treatment-Related Adverse Events (TRAEs)



No grade ≥3 hepatic dysfunction in 12 patients receiving immunotherapy within 30 days before adagrasib

Late-onset TRAEs (defined as occurring >1 year) occurred in 29 patients (43 remained on therapy >1 year) and were mostly grade 1-2

Comparing Adagrasib vs Sotorasib

	Sotorasib	Adagrasib
ORR	41%	43%
DOR	84%	80%
PFS	6.3 mos	6.9 mos
OS	12.5 mos	14.1 mos
2-yr OS	32.5%	31.3%

ORR = objective response rate; DCR = disease control rate;
PFS = progression free survival; OS = overall survival

Is there a better CNS signal with adagrasib?

	Sotorasib	Adagrasib
iORR	19%	42%
iDCR	88%	90%
iPFS	NR[a]	6.3 mos

Stable, asymptomatic, untreated CNS metastases were eligible in CodeBreak100 and KRYSTAL-1
[a] Not reported

Dy et al, *J Clin Oncol,* 2023
Negrao et al, *J Clin Oncol,* 2023
Gadgeel et al, WCLC Abstract MA06.04, 2023

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CodeBreaK 101: Safety and Efficacy of Sotorasib with Carboplatin and Pemetrexed in *KRAS* G12C–Mutated Advanced NSCLC

Jeffrey M. Clarke,[1] Enriqueta Felip,[2] Bob T. Li,[3] Jose Ruffinelli,[4] Pilar Garrido,[5] Jon Zugazagoitia,[6] Sarah B. Goldberg,[7] Suresh S. Ramalingam,[8] Ivan Victoria,[9] Sonam Puri,[10] David Gandara,[11] Tracy Varrieur,[12] Sophie Edmonds,[13] Kerry Palmer,[13] Wendy Snyder,[12] Ramaswamy Govindan,[14] Igor Rybkin[12]

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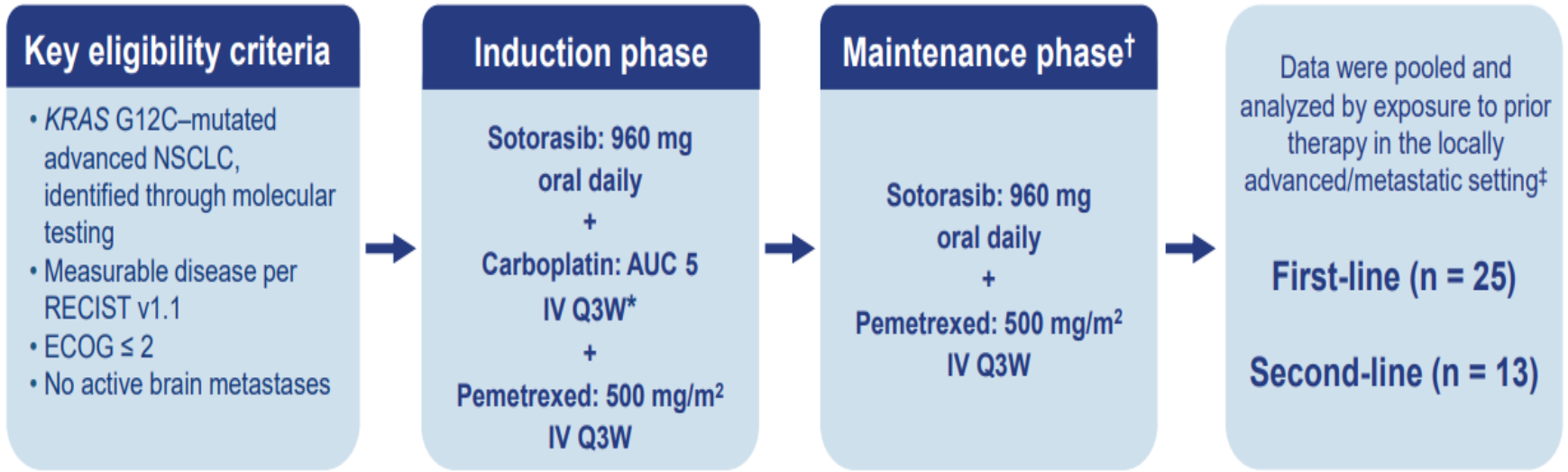
Study Schema – Phase 1b CodeBreak 101

Patient Cohorts:

- *Part 1 Cohort A:* prior PD(L)1 inhibitor and/or platinum-doublet chemotherapy
- *Part 2 Cohort A1:* no prior PD(L)1 inhibitor or platinum-doublet chemotherapy
- *Part 2 Cohort A2:* prior PD(L)1 monotherapy, platinum-doublet chemotherapy, or (neo)adjuvant chemotherapy



Primary Endpoints: Safety and tolerability (including DLT)
Secondary Endpoints: Anti-tumor efficacy (ORR, DCR, DOR, TTR, OS, PFS, duration of SD) and PK

Baseline Demographics

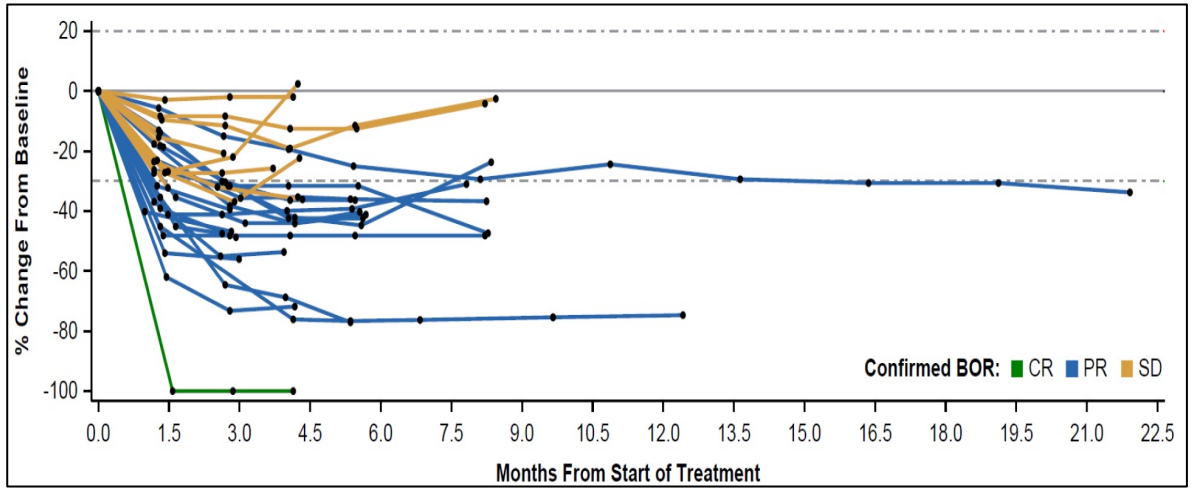
	Sotorasib + Carboplatin + Pemetrexed	
	First-line (n = 25)	Second-line (n = 13)
Median age, years (range)	64 (46, 82)	67 (44, 74)
Male, n (%)	12 (48)	8 (62)
ECOG performance score 0 / 1, n (%)	12 (48) / 13 (52)	7 (54) / 6 (46)
Stage III / IV at screening, n (%)	1 (4) / 24 (96)	0 / 13 (100)
History of brain metastasis, n (%)	4 (16)	3 (23)
Prior neoadjuvant / adjuvant chemotherapy, n (%)	2 (8)	2 (15)
Prior non-neoadjuvant / adjuvant chemotherapy, n (%)	0	6 (46)
Prior anti–PD-1 / anti–PD-L1 therapy, n (%)	0	11 (85)
PD-L1 protein expression, n (%)		
< 1%	16 (64)	4 (31)
1% – 49%	5 (20)	3 (23)
≥ 50%	3 (12)	6 (46)
Unknown	1 (4)	0

Aside from autoimmunity or patient choice, is there acceptable rationale for deferring upfront immunotherapy?

Efficacy Results

Response by Investigator Assessments*	Sotorasib + Carboplatin + Pemetrexed	
	First-line (n = 20)	Second-line (n = 13)
ORR, n (%)	13 (65)†	7 (54)
Best overall response, n (%)		
Complete response	0	1 (8)
Partial response	13 (65)	6 (46)
Stable disease	7 (35)	4 (31)
Progressive disease	0	1 (8)
Not evaluable / not done	0	1 (8)
DCR (95% CI)	20 (100) (83.2, 100)	11 (85) (54.6, 98.1)

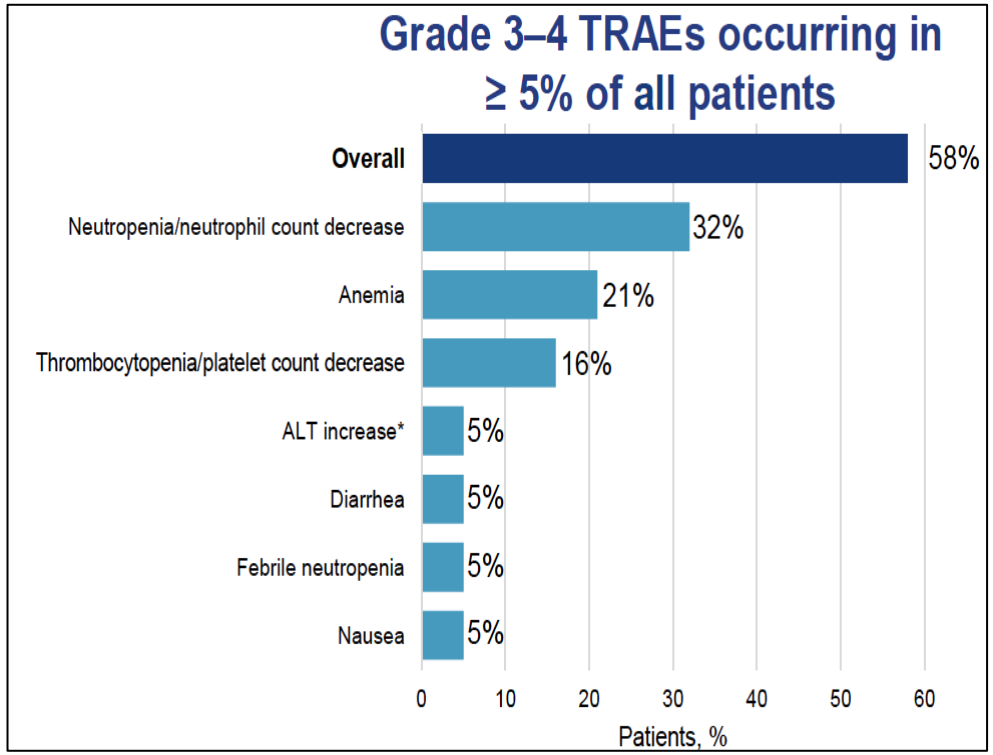
Favorable ORR compared to historical controls in the non-immunotherapy era



PFS and OS data have not matured but durable responses observed

Treatment-Related Adverse Events (TRAEs)

TRAEs, n (%)	Sotorasib + Carboplatin + Pemetrexed	
	First-line (n = 25)	Second-line (n = 13)
Any grade	23 (92)	13 (100)
Grade 1	4 (16)	1 (8)
Grade 2	7 (28)	2 (15)
Grade 3	10 (40)	8 (62)
Grade 4	2 (8)	2 (15)
TRAEs leading to discontinuation of any treatment	3 (12)	4 (31)
Discontinuation of sotorasib	2 (8)	2 (15)
Discontinuation of carboplatin	1 (4)	2 (15)
Discontinuation of pemetrexed	3 (12)	3 (23)



Conclusions

- In the setting of FLAURA2, there is likely to be increased interest in other TKI-chemotherapy combinations.
- However, would recommend caution in pursuing this at the expense of immunotherapy for driver mutations other than *EGFR/ALK/ROS1* given the known benefit of immunotherapy-based regimens in the front-line metastatic setting and the known association of *KRAS* G12C with smoking history.
- The combination of chemotherapy plus sotorasib had an acceptable safety profile, and if studied further, may be best done so in the post-immunotherapy setting.

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KontRASt-01: Preliminary safety and efficacy of JDQ443 + TNO155 in patients with advanced, *KRAS G12C*-mutated solid tumors

Marcelo V Negrao,[1] Philippe Cassier,[2] Benjamin Solomon,[3] Martin Schuler,[4] Kristoffer Staal Rohrberg,[5] Sara Cresta,[6] Christophe Dooms,[7] Daniel SW Tan,[8] Herbert HF Loong,[9] Alessio Amatu,[10] Kimberly Krueger Assmann,[11] Lauren Fairchild,[12] Laurent Sansregret,[13] Liqiong Fan,[12] Anna F Farago,[12] Byoung Chul Cho[14]

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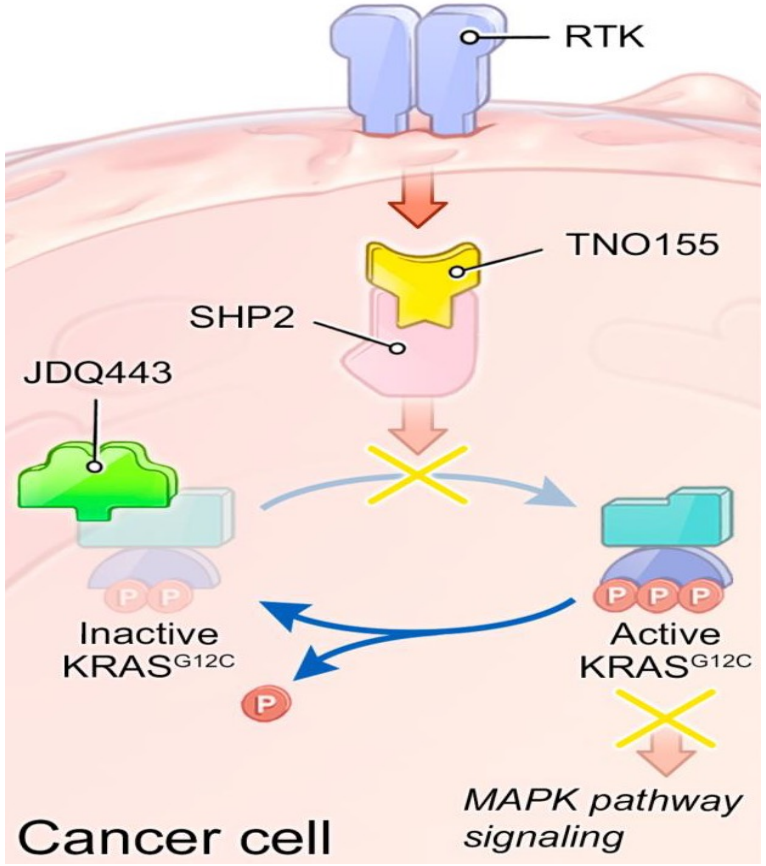
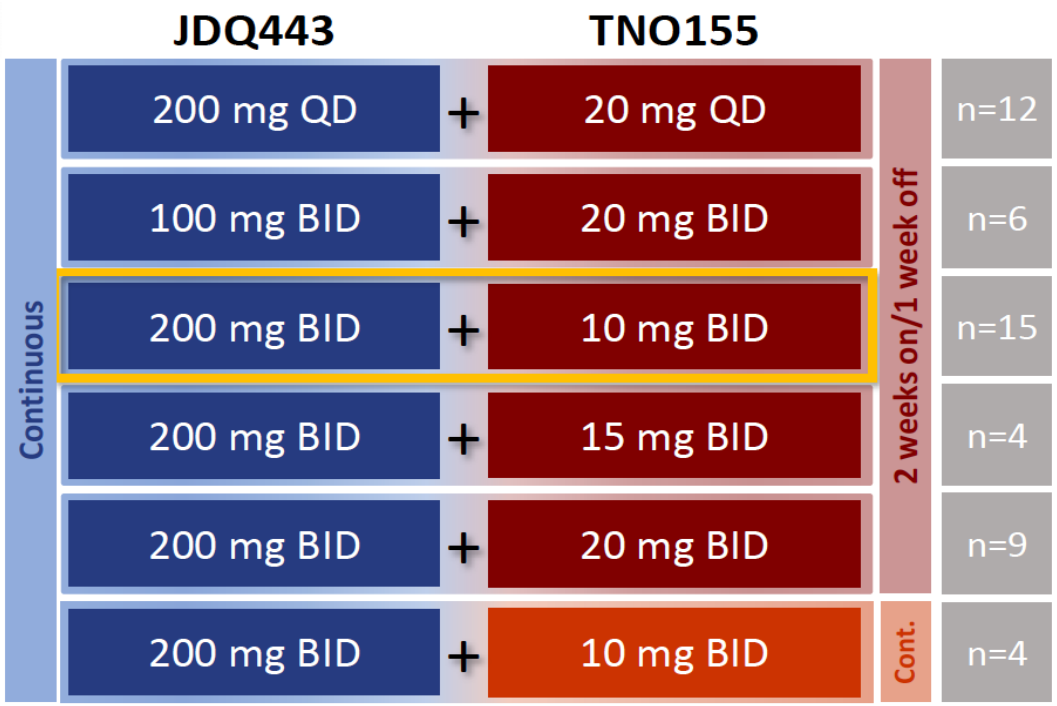
9. Department of Clinical Oncology, The Chinese University of Hong Kong, Hong Kong; 10. Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy;
11. Novartis Institutes for BioMedical Research, East Hanover, NJ, USA; 12. Novartis Institutes for BioMedical Research, Cambridge, MA, USA;
13. Novartis Institutes for BioMedical Research, Basel, Switzerland; 14. Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea.

Rationale for SHP2 Inhibition



- SHP2 = Src homology region 2-containing protein tyrosine phosphatase 2 (encoded by *PTPN11* gene)
- Serves regulatory role in many signaling pathways including RAS/MAPK/ERK
- In the case of KRAS, activation of SHP2 leads to downstream activation of KRAS by converting it from its inactive GDP-bound state to an active GTP-bound state
- Based on this rationale, the safety and efficacy of a SHP2 inhibitor (TNO155) combined with a KRAS G12 inhibitor (JDQ443) was assessed

Dosing and Treatment-Related Adverse Events (TRAEs)



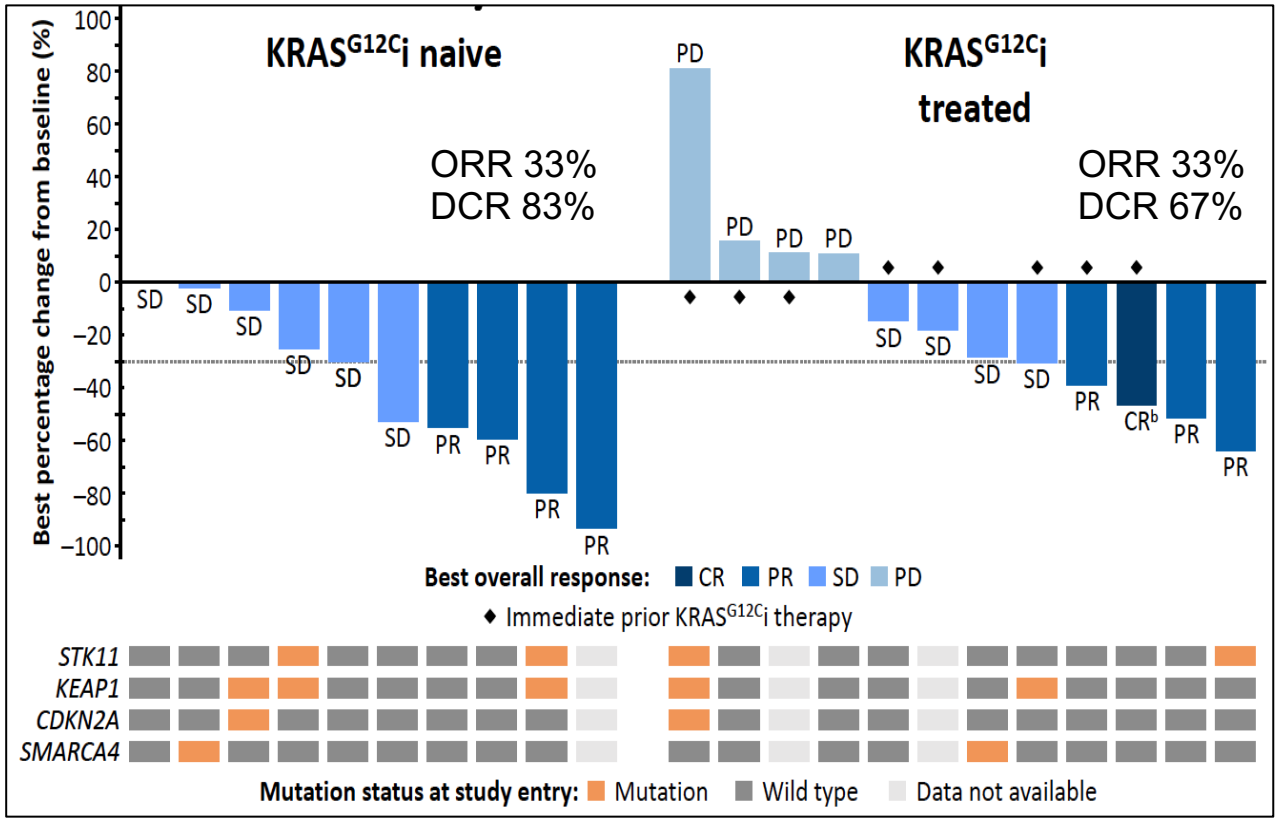
** TRAEs occurring in ≥15% of patients are shown **

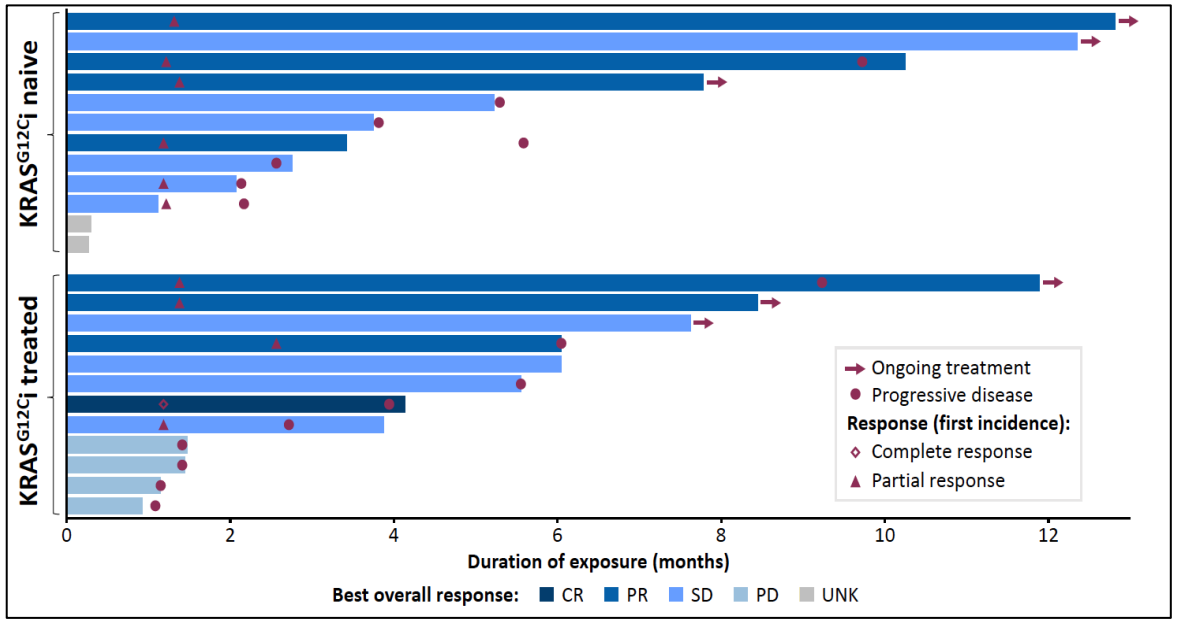
	All dose levels, pooled (N=50)		JDQ443 200 mg BID continuous + TNO155 10 mg BID 2 weeks on/1 week off (n=15)	
	All grades	Grade ≥3	All grades	Grade ≥3
Patients with any TRAE, n (%)	**44 (88.0)**	**18 (36.0)**	**14 (93.3)**	**4 (26.7)**
Peripheral edema	20 (40.0)	–	6 (40.0)	–
Neutropenia	15 (30.0)	7 (14.0)	2 (13.3)	1 (6.7)
Thrombocytopenia	14 (28.0)	4 (8.0)	4 (26.7)	–
Diarrhea	13 (26.0)	1 (2.0)	4 (26.7)	1 (6.7)
Anemia	12 (24.0)	4 (8.0)	4 (26.7)	–
Fatigue	9 (18.0)	–	5 (33.3)	–
Increased blood creatine phosphokinase	8 (16.0)	1 (2.0)	1 (6.7)	–

- No episodes of pneumonitis seen
- ALT and/or AST increased in 10-12% (grade ≥3 in 2%)

Dosing and Treatment-Related Adverse Events (TRAEs)

N = 24 (median 3 prior lines of therapy)





Conclusions

- SHP2 is a novel target in the treatment of metastatic NSCLC.
- In the case of heavily-treated *KRAS* G12C-positive NSCLC, combination of a SHP2 inhibitor plus a KRAS inhibitor resulted in a promising response rate of 30% with durable responses ongoing.
- Novel therapies are needed in the treatment of *KRAS* G12C-positive NSCLC, both before and after existing KRAS inhibitors (eg, sotorasib, adagrasib), and SHP2 inhibition in this setting warrants further study.

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Trastuzumab Deruxtecan in Patients With *HER2*-Mutant Metastatic Non–Small Cell Lung Cancer: Primary Results of DESTINY-Lung02

Pasi A. Jänne,[a] Yasushi Goto, Toshio Kubo, Kiichiro Ninomiya, Sang-We Kim, David Planchard, Myung-Ju Ahn, Egbert F. Smit, Adrianus Johannes de Langen, Maurice Pérol, Elvire Pons-Tostivint, Silvia Novello, Hidetoshi Hayashi, Junichi Shimizu, Dong-Wan Kim, Kaline Pereira, Fu-Chih Cheng, Ayumi Taguchi, Yingkai Cheng, and Koichi Goto

On behalf of the DESTINY-Lung02 investigators

Rationale and Study Schema

DESTINY-Lung01: Enhertu 6.4 mg/kg

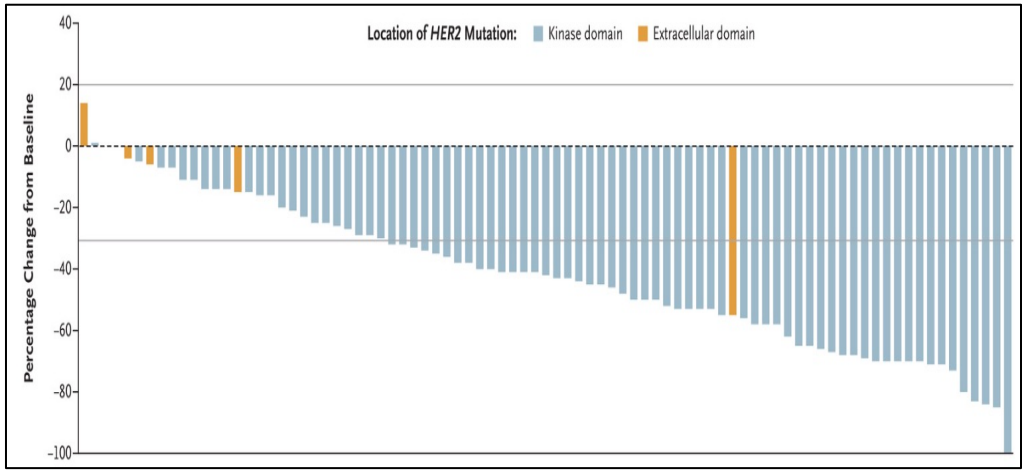


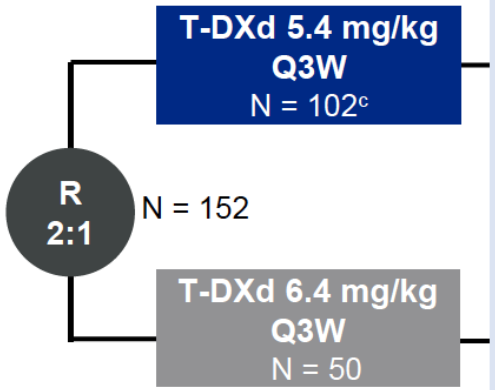
Table S5. Adjudicated Drug-related Interstitial Lung Disease.

	Patients (N = 91)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Adjudicated drug-related interstitial lung disease, n (%)*	3 (3.3)	15 (16.5)	4 (4.4)	0	2 (2.2)†	24 (26.4)

DESTINY-Lung02

Key Eligibility Criteria[a]
- Metastatic *HER2*m[b] NSCLC
- ≥1 prior anticancer therapy (2L+), including platinum-based chemotherapy
- Measurable disease per RECIST v1.1
- ECOG PS of 0 or 1

Stratification Factor:
- Prior anti–PD-(L)1 treatment

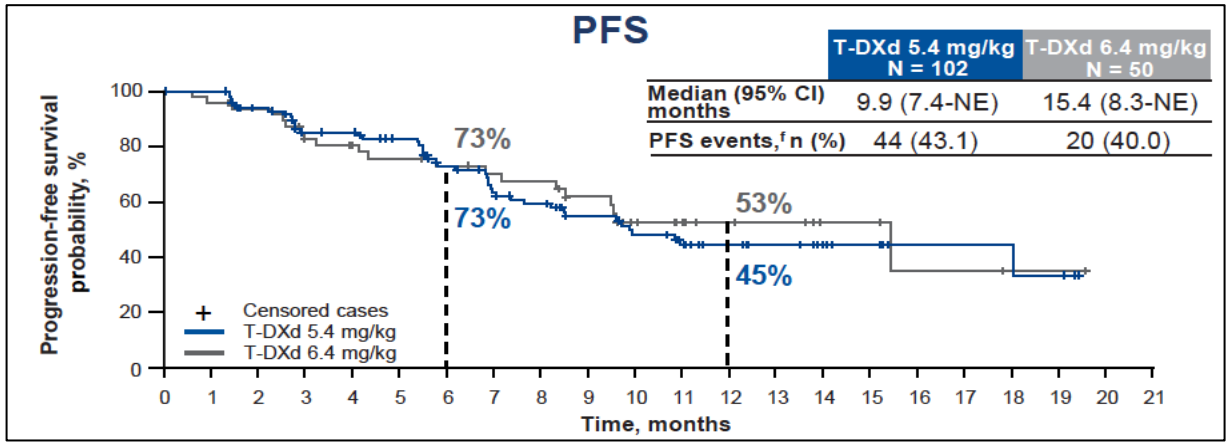


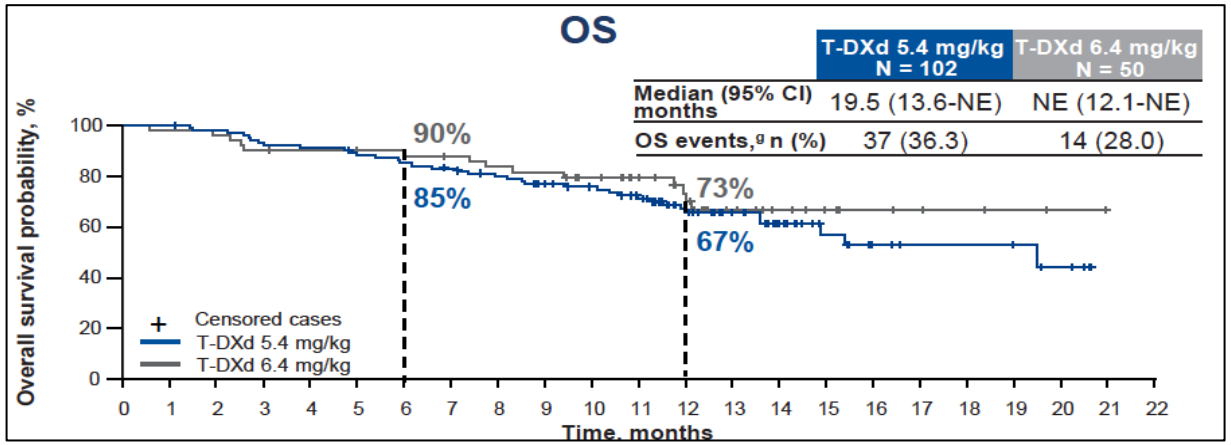
Primary Endpoint
- Confirmed ORR by BICR

Secondary Endpoints
- Confirmed ORR by INV
- DoR by BICR and INV
- DCR by BICR and INV
- PFS by BICR and INV
- OS
- Safety

Patients and investigators were blinded to the dose level

Comparable Efficacy and Survival Between Dose Levels



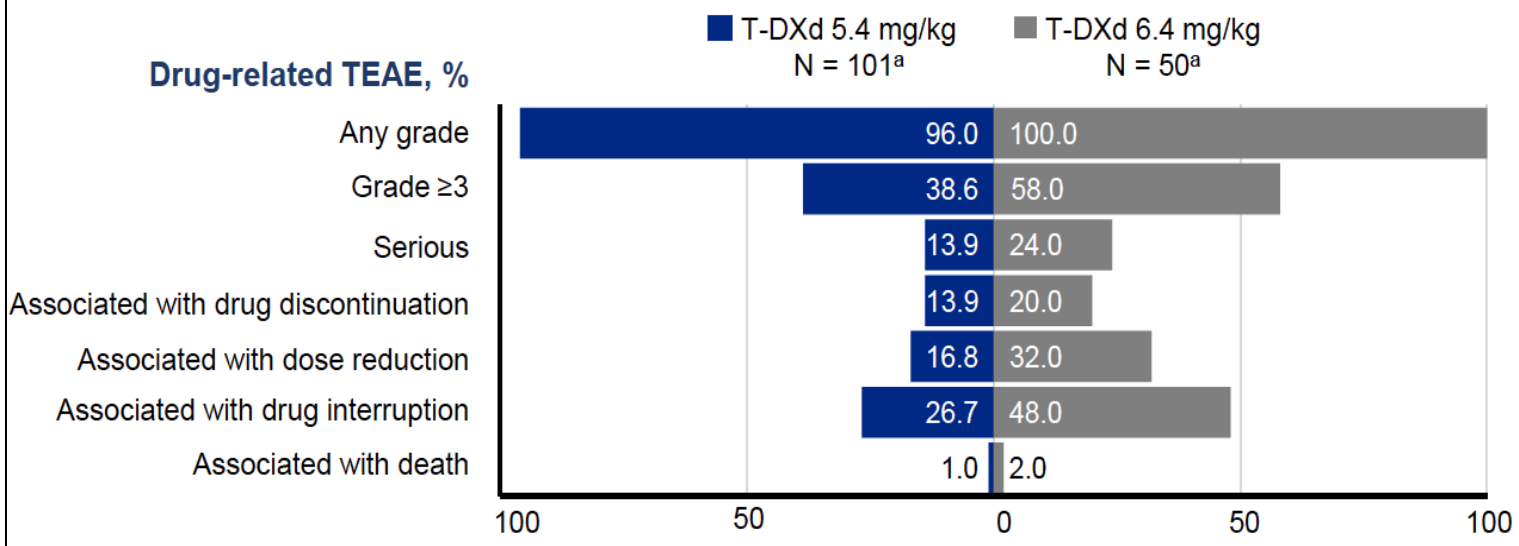


Efficacy summary	T-DXd 5.4 mg/kg N = 102	T-DXd 6.4 mg/kg N = 50
Confirmed ORR,[a] n (%) [95% CI]	**50 (49.0)** [39.0-59.1]	**28 (56.0)** [41.3-70.0]
CR | PR	1 (1.0) | 49 (48.0)	2 (4.0) | 26 (52.0)
SD | PD	45 (44.1) | 4 (3.9)	18 (36.0) | 2 (4.0)
Non-evaluable[b]	3 (2.9)	2 (4.0)
DCR,[c] n (%) [95% CI]	95 (93.1) [86.4-97.2]	46 (92.0) [80.8-97.8]
Median DoR,[d,e] months (95% CI)	16.8 (6.4-NE)	NE (8.3-NE)
Median TTIR,[d] months (range)	1.8 (1.2-7.0)	1.6 (1.2-11.2)
Median follow-up, months (range)	11.5 (1.1-20.6)	11.8 (0.6-21.0)

ORR = objective response rate; DCR = disease control rate; DOR = duration of response; TTIR = time to initial response

Safety Comparison Between Dose Levels

Overall Safety



Adjudicated Drug-Related ILD

Adjudicated as drug-related ILD	T-DXd 5.4 mg/kg N = 101[a]	T-DXd 6.4 mg/kg N = 50[a]
Any grade, n (%)	**13 (12.9)**	**14 (28.0)**
Grade 1	4 (4.0)	4 (8.0)
Grade 2	7 (6.9)	9 (18.0)
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	1 (1.0)	1 (2.0)

Rates of most side-effects, including drug-related interstitial lung disease, were lower in the T-DXd 5.4 mg/kg group

Conclusions

- Trastuzumab-deruxtecan (TDXd) remains an important option in the treatment of patients with *HER2*-mutated NSCLC.
- TDXd at 5.4 mg/kg q3 weeks appears to be better tolerated without a significant difference in efficacy or survival compared to the higher 6.4 mg/kg q3 week dosing.
- While rates of pneumonitis may be lower at the 5.4 mg/kg q3 week dose, a high index of suspicion and careful monitoring remain necessary in all patients.