Lung Cancer UPDATES
ASCO HIGHLIGTHS
29-31 MAYO 2020

Iniciativa científica de:
GECP lung cancer research

Enfermedad avanzada: tratamiento antidiana en mutaciones infrecuentes

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MET alterations

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tepotinib in Non–Small-Cell Lung Cancer with *MET* Exon 14 Skipping Mutations

P.K. Paik, E. Felip, R. Veillon, H. Sakai, A.B. Cortot, M.C. Garassino, J. Mazieres, S. Viteri, H. Senellart, J. Van Meerbeeck, J. Raskin, N. Reinmuth, P. Conte, D. Kowalski, B.C. Cho, J.D. Patel, L. Horn, F. Griesinger, J.-Y. Han, Y.-C. Kim, G.-C. Chang, C.-L. Tsai, J.C.-H. Yang, Y.-M. Chen, E.F. Smit, A.J. van der Wekken, T. Kato, D. Juraeva, C. Stroh, R. Bruns, J. Straub, A. Johne, J. Scheele, J.V. Heymach, and X. Le

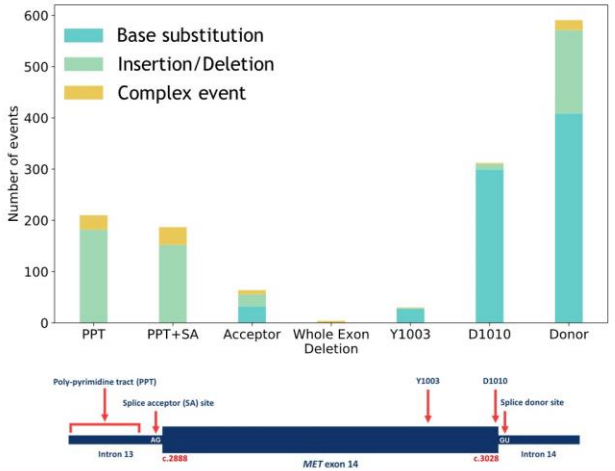
MET alterations

Characterization of 1,387 NSCLCs with *MET* exon 14 (*MET*ex14) skipping alterations (SA) and potential acquired resistance (AR) mechanisms

Mark Awad[1], Jessica Lee[2], Russell Madison[2], Anthony Classon[2], Jamie Kmak[2], Garrett Frampton[2], Brian Alexander[2], Jeffrey Venstrom[2], Alexa B. Schrock[2]

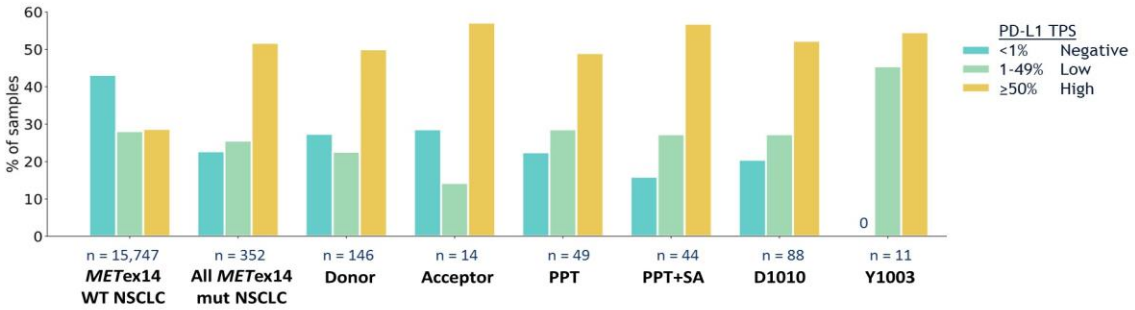
[1]Dana-Farber Cancer Institute, Boston, MA; [2]Foundation Medicine, Inc., Cambridge, MA

*MET*ex14 alterations in 1,387 NSCLC patient samples



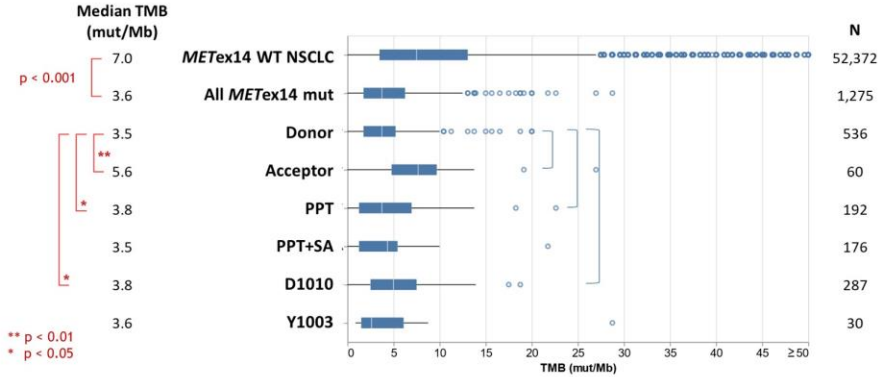
- NGS-based hybrid-capture genomic profiling of tumor DNA from 60,495 patients with NSCLC, including baiting of all *MET* exons
- *MET*ex14 alts were present in samples from 1,387 (2.3%) of patients with NSCLC
  - 2.3% tissue (n=53,681)
  - 1.6% ctDNA (n=5,988)
- >500 unique *MET*ex14 alts included base substitutions, indels, deletions and complex events spanned multiple functional sites resulting in exons 14 skipping, deletion, or mutation at Y1003

PD-L1 expression across *MET*ex14 NSCLC



- *MET*ex14 altered NSCLC is enriched for high (≥50%) PD-L1 positivity vs WT NSCLC (48% vs 29%, p=5.5E-19)
- PD-L1 positivity was relatively similar across *MET*ex14 alteration functional site subsets
- For all *MET*ex14 NSCLC cases, there was no association of TMB and PD-L1 expression (P=0.76)

TMB distribution across *MET*ex14 NSCLC



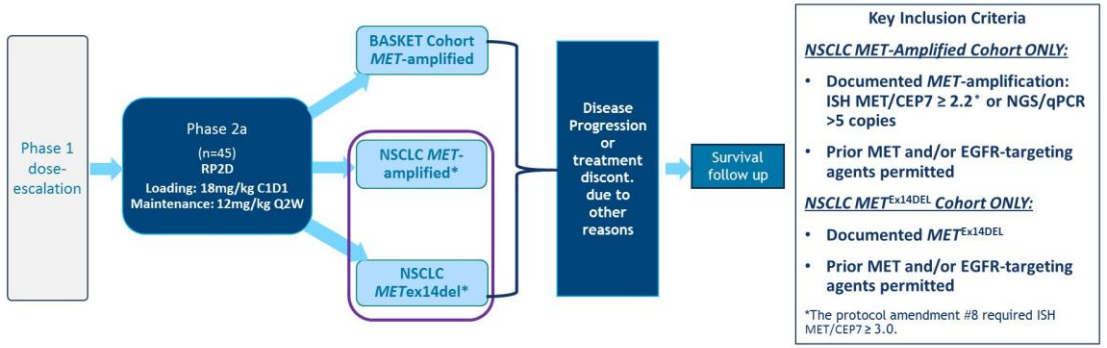
- *MET*ex14-altered NSCLC had significant lower TMB vs *MET*ex14-wild-type NSCLC
- TMB of donor site samples was significantly lower than TMB of acceptor, PPT, and D1010 samples

MET alterations

Safety and preliminary clinical activity of the MET antibody mixture Sym015 in advanced non-small cell lung cancer (NSCLC) patients with *MET*-amplification/exon 14 deletion (*MET*$^{Amp/Ex14\Delta}$)

D.R. Camidge, F. Janku, A. Martinez Bueno, D. Catenacci, J. Lee, S.H. Lee, A. Dowlati, K. Rohrberg, A. Navarro, Y.W. Moon, M. Awad, R. Heist, T. Poulsen, Arielle Yablonovitch, Lindsay Fosler, H. Rudbæk, Frank Nygaard, D. L. Woods, R.P. Dalal, E. Felip

Clinical Trial Design



*Two NSCLC cohorts were added after preliminary data review of patients in basket cohort.

Sym015-01 Phase 2a data indicate favorable safety profile

Treatment Emergent AE >10%	Phase 2a (n=45) n (%)	NSCLC (n=20) n (%)
All	42 (93.3%)	19 (95.0%)
Oedema Peripheral	11 (24.4%)	10 (50.0%)
Fatigue	10 (22.2%)	4 (20.0%)
Nausea	10 (22.2%)	4 (20.0%)
Constipation	9 (20.0%)	4 (20.0%)
Decreased Appetite	9 (20.0%)	3 (15.0%)
Cough	8 (17.8%)	6 (30.0%)
Abdominal Pain	7 (15.6%)	1 (5.0%)
Anaemia	7 (15.6%)	1 (5.0%)
Pyrexia	7 (15.6%)	3 (15.0%)
Hypoalbuminaemia	6 (13.3%)	1 (5.0%)
Aspartate Aminotransferase Increased	5 (11.1%)	4 (20.0%)
Back Pain	5 (11.1%)	2 (10.0%)
Dyspepsia	5 (11.1%)	3 (15.0%)
Dyspnoea	5 (11.1%)	4 (20.0%)

Treatment Related AE >5%	Phase 2a (n=45) n (%)	NSCLC (n=20) n (%)
All	22 (48.9%)	11 (55.0%)
Oedema Peripheral	7 (15.6%)	7 (35.0%)
Fatigue	6 (13.3%)	1 (5.0%)
Aspartate Aminotransferase Increased	4 (8.9%)	3 (15.0%)
Nausea	4 (8.9%)	2 (10.0%)
Abdominal Pain	3 (6.7%)	-
Asthenia	3 (6.7%)	2 (10.0%)
Decreased Appetite	3 (6.7%)	2 (10.0%)
Pruritus	3 (6.7%)	1 (5.0%)

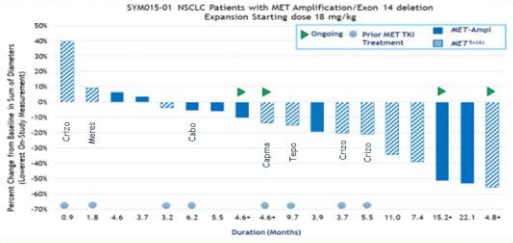
- **Grade ≥ 3 related AEs reported in 6* of 45 (13.3%) pts:**
  - Anasarca and hypoalbuminemia
  - Colitis and septic shock
  - Hypophosphatemia
  - Amylase increase
  - Peripheral edema (NSCLC pt.)
  - Elevated LFTs (NSCLC pt.)
- **Dose reductions- 1 patient (NSCLC); dose reduced to 6 mg/kg q2w.**
- **No reports of treatment discontinuation due to adverse events**

*2 patients experienced 2 Grade ≥ 3 related AEs

Data Cut Date: 14Apr2020

Tumor Response: NSCLC (n=20)

	ORR n (%)	DCR n (%)	DoR (months) median (95% CI)	mPFS (months) median (95% CI)
Overall (n=20)	**5 (25%)**	**16 (80.0%)**	**13.8 (3.8-18.4)**	**5.5 (3.8-9.7)**
MET TKI Naïve (n=10)	**5 (50%)**	**10 (100%)**	**13.8 (3.8-18.4)**	**7.4 (3.4-21.9)**
MET$^{Ex14\Delta}$ (n=3)	3 (100%)	3 (100%)	6.5 (3.8-9.2)	9.2 (7.4-11.0)
MET-Amplification (n=7)	2 (28.6%)	7 (100%)	18.4 (NE)	5.5 (3.4-21.9)
MET TKI pre-treated (n=10)	-	**6 (60.0%)**	-	**5.4 (1.2-9.7)**
MET$^{Ex14\Delta}$ (n=?)	-	5 (55.6%)	-	5.4 (1.2-9.7)
MET-Amplification (n=?)	-	1 (100%)	-	6.2 (NE)



- Prior Met TKI treated-*MET*$^{Ex14\Delta}$ subgroup: mOS 9.1 months
- mOS not reached for overall NSCLC population and other subgroups
- Range of OS- 0.13, 34.79 months

Data Cut Date: 14Apr2020

MET alterations

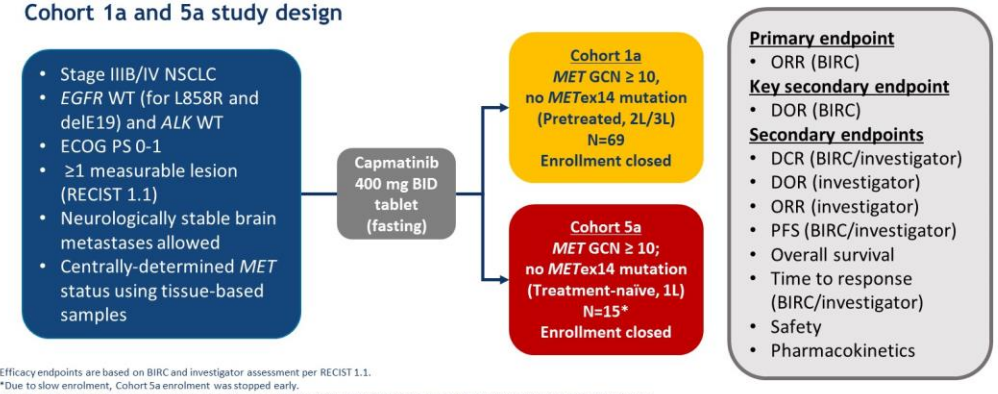
Capmatinib in patients with high-level *MET*-amplified advanced non–small cell lung cancer (NSCLC): Results from the phase 2 GEOMETRY mono-1 study

Juergen Wolf,[1] Tobias R. Overbeck,[2] Ji-Youn Han,[3] Maximilian Hochmair,[4] Filippo de Marinis,[5] Kadoaki Ohashi,[6] Egbert F. Smit,[7] Danielle Power,[8] Edward B. Garon,[9] Harry J. M. Groen,[10] Daniel S. W. Tan,[11] Maeve Waldron-Lynch,[12] Sylvie Le Mouhaer,[13] Ngozi Nwana,[14] Monica Giovannini,[14] Rebecca S. Heist[15]

[1]Center for Integrated Oncology, University Hospital Cologne, Cologne, Germany; [2]University Medical Center Göttingen, Göttingen, Germany; [3]National Cancer Center, Gyeonggi-do, Republic of Korea; [4]Department of Respiratory and Critical Care Medicine, Vienna North Hospital, Karl Landsteiner Institute of Lung Research and Pulmonary Oncology, Vienna, Austria; USA; [5]Istituto Europeo di Oncologia IRCCS, Milan, Italy; [6]Okayama University Hospital, Okayama, Japan; [7]Netherlands Cancer Institute, Amsterdam, The Netherlands; [8]Imperial College Healthcare NHS Trust, London, United Kingdom; [9]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [10]University of Groningen and University Medical Center Groningen, Groningen, The Netherlands; [11]National Cancer Centre Singapore, Singapore; [12]Novartis Pharma AG, Basel, Switzerland; [13]Novartis Pharma S.A.S, Rueil-Malmaison, France; [14]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [15]Massachusetts General Hospital, Boston, MA, USA.

GEOMETRY mono-1: An open-label international multicohort phase 2 study

Cohort 1a and 5a study design



Efficacy endpoints are based on BIRC and investigator assessment per RECIST 1.1.
*Due to slow enrolment, Cohort 5a enrolment was stopped early.
Data cut off for this analysis: Jan 6, 2020; at time of data cut off, 3 patients (4.3%) in Cohort 1a were still receiving treatment, none in Cohort 5a.
1L/2L/3L, first/second/third line; *ALK*, anaplastic lymphoma kinase; BID, twice daily; BIRC, Blinded Independent Review Committee; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; GCN, gene copy number; *MET*ex14, *MET* exon 14 skipping mutation; NSCLC, non-small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; RT-PCR, reverse transcription polymerase chain reaction; WT, wild-type.

Best overall response (Cohorts 1a and 5a)

Best overall response, n (%)	Cohort 1a (2/3L, GCN ≥ 10) (N=69)		Cohort 5a (1L, GCN ≥ 10) (N=15)	
	BIRC	Investigator	BIRC	Investigator
Complete response (CR)	1 (1.4)	1 (1.4)	0	0
Partial response (PR)	19 (27.5)	18 (26.1)	6 (40.0)	6 (40.0)
Stable disease (SD)	28 (40.6)	23 (33.3)	4 (26.7)	5 (33.3)
Non-CR/non-PD	1 (1.4)	0	0	0
Progressive disease (PD)	12 (17.4)	21 (30.4)	4 (26.7)	3 (20.0)
Not evaluable*	8 (11.6)	6 (8.7)	1 (6.7)	1 (6.7)
ORR,† % (95% CI)	**29.0 (18.7-41.2)**	**27.5 (17.5-39.6)**	**40.0 (16.3-67.7)**	**40.0 (16.3-67.7)**
DCR,‡ % (95% CI)	**71.0 (58.8-81.3)**	**60.9 (48.4-72.4)**	**66.7 (38.4-88.2)**	**73.3 (44.9-92.2)**

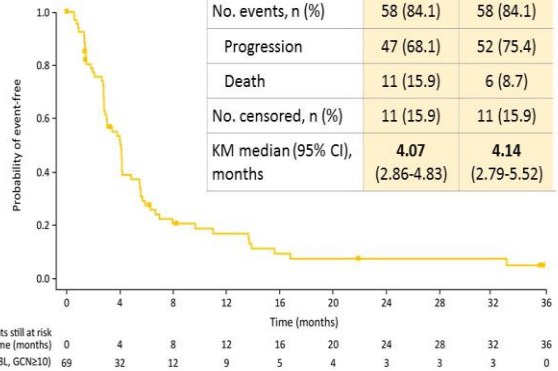
*All other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or progression within the first 12 weeks).
†ORR: Complete or partial response.
‡DCR: Patients who achieved complete response, partial response, stable disease or non-complete response/non-progressive disease.
1L/2L/3L, first/second/third-line; BIRC, Blinded Independent Review Committee; CI, confidence interval; DCR, disease control rate; GCN, gene copy number; ORR, overall response rate.

MET alterations

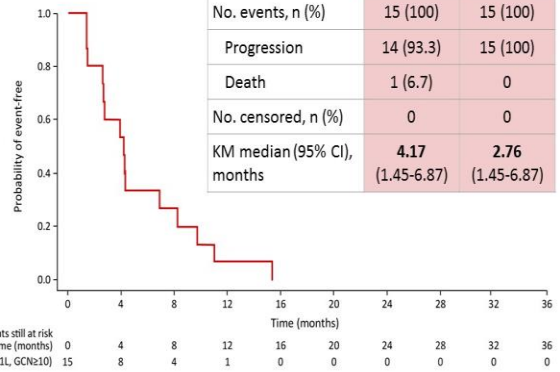
Progression-free survival assessed by the BIRC

Median PFS: 4.07 months in pretreated patients and 4.17 months in treatment-naive patients

	Cohort 1a (2/3L, GCN ≥ 10) (N=69)	
	BIRC	Investigator
No. events, n (%)	58 (84.1)	58 (84.1)
Progression	47 (68.1)	52 (75.4)
Death	11 (15.9)	6 (8.7)
No. censored, n (%)	11 (15.9)	11 (15.9)
KM median (95% CI), months	**4.07** (2.86-4.83)	**4.14** (2.79-5.52)



	Cohort 5a (1L, GCN ≥ 10) (N=15)	
	BIRC	Investigator
No. events, n (%)	15 (100)	15 (100)
Progression	14 (93.3)	15 (100)
Death	1 (6.7)	0
No. censored, n (%)	0	0
KM median (95% CI), months	**4.17** (1.45-6.87)	**2.76** (1.45-6.87)

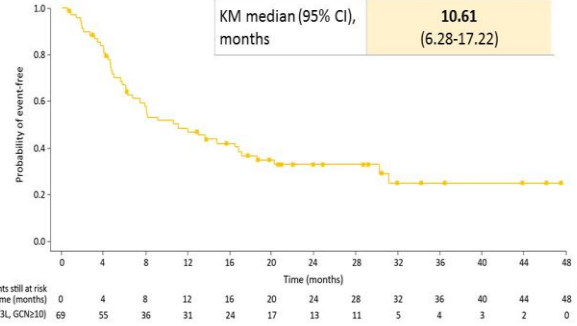


1L/2L/3L, first/second/third-line; BIRC, Blinded Independent Review Committee; GCN, gene copy number; PFS, progression-free survival.

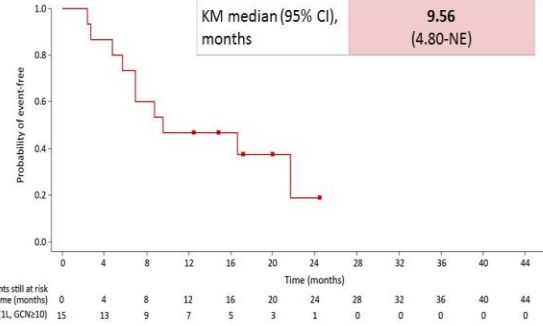
Overall survival

Median OS: 10.61 months in pretreated patients and 9.56 months in treatment-naive patients

	Cohort 1a (2/3L, GCN ≥ 10) (N=69)
No. deaths, n (%)	45 (65.2)
No. censored, n (%)	24 (34.8)
KM median (95% CI), months	**10.61** (6.28-17.22)



	Cohort 5a (1L, GCN ≥ 10) (N=15)
No. deaths, n (%)	10 (66.7)
No. censored, n (%)	5 (33.3)
KM median (95% CI), months	**9.56** (4.80-NE)



1L/2L/3L, first/second/third-line; GCN, gene copy number; NE, not estimated; OS, overall survival.

HER2 mutations

Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients With HER2-Mutated Metastatic Non-Small Cell Lung Cancer: Interim Results of DESTINY-Lung01

Egbert F. Smit, Kazuhiko Nakagawa, Misako Nagasaka, Enriqueta Felip, Yasushi Goto, Bob T. Li, Jose M. Pacheco, Haruyasu Murakami, Fabrice Barlesi, Andreas Saltos, Maurice Perol, Hibiki Udagawa, Kapil Saxena, Ryota Shiga, Ferdinand Guevara, Suddhasatta Acharyya, Javad Shahidi, David Planchard, Pasi A. Jänne

On behalf of the DESTINY-Lung01 investigators

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On behalf of the DESTINY-Lung01 investigators

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HER2 mutations

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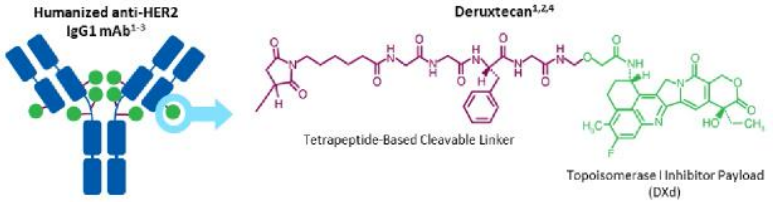
On behalf of the DESTINY-Lung01 investigators

T-DXd is a Novel ADC Designed to Deliver an Optimal Antitumor Effect

T-DXd is an ADC with 3 components:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker



Payload mechanism of action: topoisomerase I inhibitor
High potency of payload
High drug to antibody ratio ≈ 8
Payload with short systemic half-life
Stable linker-payload
Tumor-selective cleavable linker
Membrane-permeable payload

The clinical relevance of these features is under investigation.
ADC, antibody-drug conjugate.
1. Nakada T, et al. *Chem Pharm Bull* (Tokyo). 2019;67(3):173-185. 2. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. 3. Trail PA, et al. *Pharmacol Ther*. 2018;181:126-142. 4. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

DESTINY-Lung01 Study Design

An open-label, multicenter, phase 2 study (NCT03505710)

Patients

- Unresectable/metastatic nonsquamous NSCLC
- Relapsed/refractory to standard treatment
- HER2-expressing or HER2-activating mutation[a]
- No prior HER2-targeted therapy, except pan-HER TKIs

Cohort 1 (n = 42)
HER2 expressing (IHC 3+ or IHC 2+)

Cohort 2 (n = 42)
HER2 mutated

T-DXd 6.4 mg/kg q3w

Primary endpoint

- Confirmed ORR by independent central review

Data cutoff: November 25, 2019

- 45.2% of patients (19/42) in Cohort 2 remained on treatment
- 54.8% discontinued, primarily for progressive disease and adverse events (21.4% each)

[a] Based on local assessment of archival tissue.

DESTINY-Lung01 HER2-Mutated NSCLC

Baseline Characteristics

	Patients (N = 42)
Age, median (range), years	63.0 (34-83)
< 65 years, %	59.5
Female, %	64.3
Region, %	
Asia / North America / Europe	35.7 / 31.0 / 33.3
ECOG performance status 0 / 1, %	23.8 / 76.2
HER2 mutation, %	
Kinase domain	90.5
Extracellular domain	4.8
Not reported	4.8
Presence of CNS metastases, %	45.2

HER2 mutations

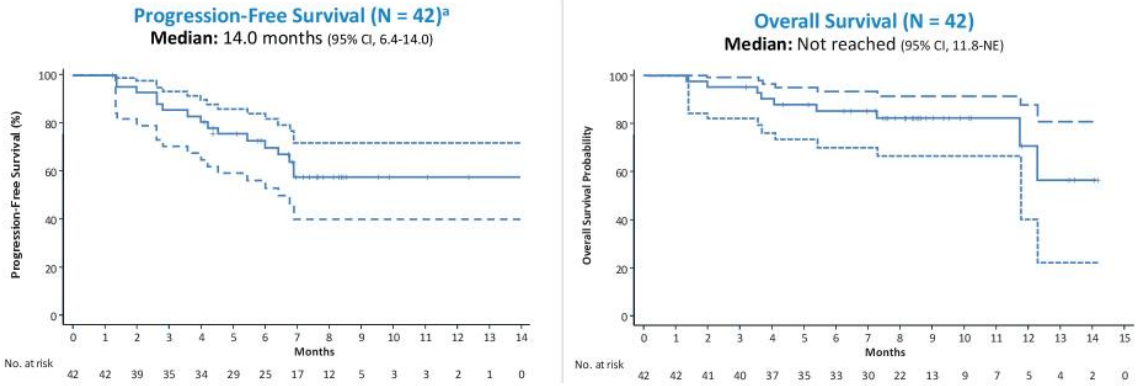
DESTINY-Lung01 HER2-Mutated NSCLC

Efficacy Results

	Patients (N = 42)
Confirmed ORR by ICR	**61.9% (n = 26)** (95% CI, 45.6%-76.4%)
CR	2.4% (n = 1)
PR	59.5% (n = 25)
SD	28.6% (n = 12)
PD	4.8% (n = 2)
Not evaluable	4.8% (n = 2)
Disease control rate	90.5% (95% CI, 77.4%-97.3%)
Duration of response, median	Not reached (95% CI, 5.3 months-NE)
PFS, median	14.0 mo (95% CI, 6.4-14.0 months)

DESTINY-Lung01 HER2-Mutated NSCLC

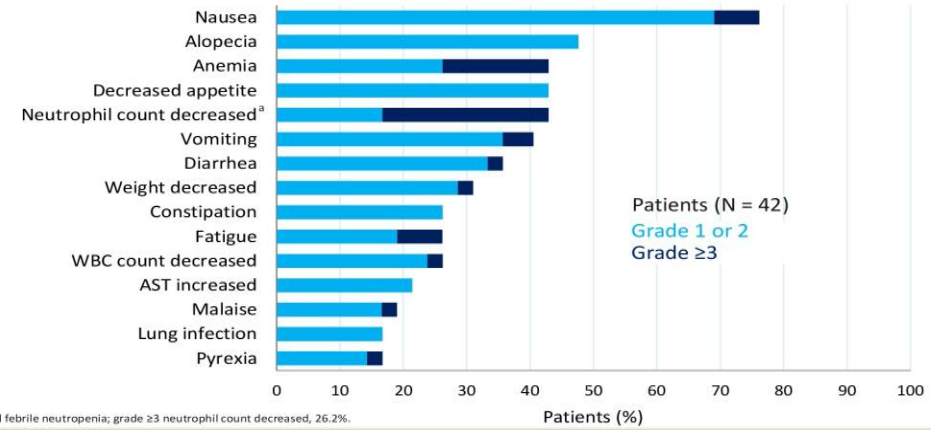
Progression-Free and Overall Survival



[a] Patients were censored if they discontinued treatment; the median is estimated by Kaplan-Meier analysis. Median follow-up, 8.0 months (range, 1.4-14.2 months). Dashed lines indicate upper and lower 95% CI.

DESTINY-Lung01 HER2-Mutated NSCLC

Treatment-Emergent Adverse Events in >15% of Patients



[a] 2 patients had febrile neutropenia; grade ≥3 neutrophil count decreased, 26.2%.

DESTINY-Lung01 HER2-Mutated NSCLC

AEs of Special Interest: Interstitial Lung Disease (ILD)

	All Patients (N = 42)					
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade/ Total
Interstitial lung disease	0[a]	5 (11.9)	0	0	0	5 (11.9)

- Median time to onset of investigator-reported ILD was at 86 days (range, 41-255 days)
- 4 patients had drug withdrawn and 1 had drug interrupted
- All patients received steroid treatment
- 2 patients recovered, 1 recovered with sequelae, 1 was recovering, and 1 had not recovered by data-cutoff
- No grade 5 ILD was observed in this cohort

Drug-related; ILD was determined by an Independent ILD Adjudication Committee based on 44 preferred terms.
[a] 1 case of potential grade 1 ILD was pending adjudication.