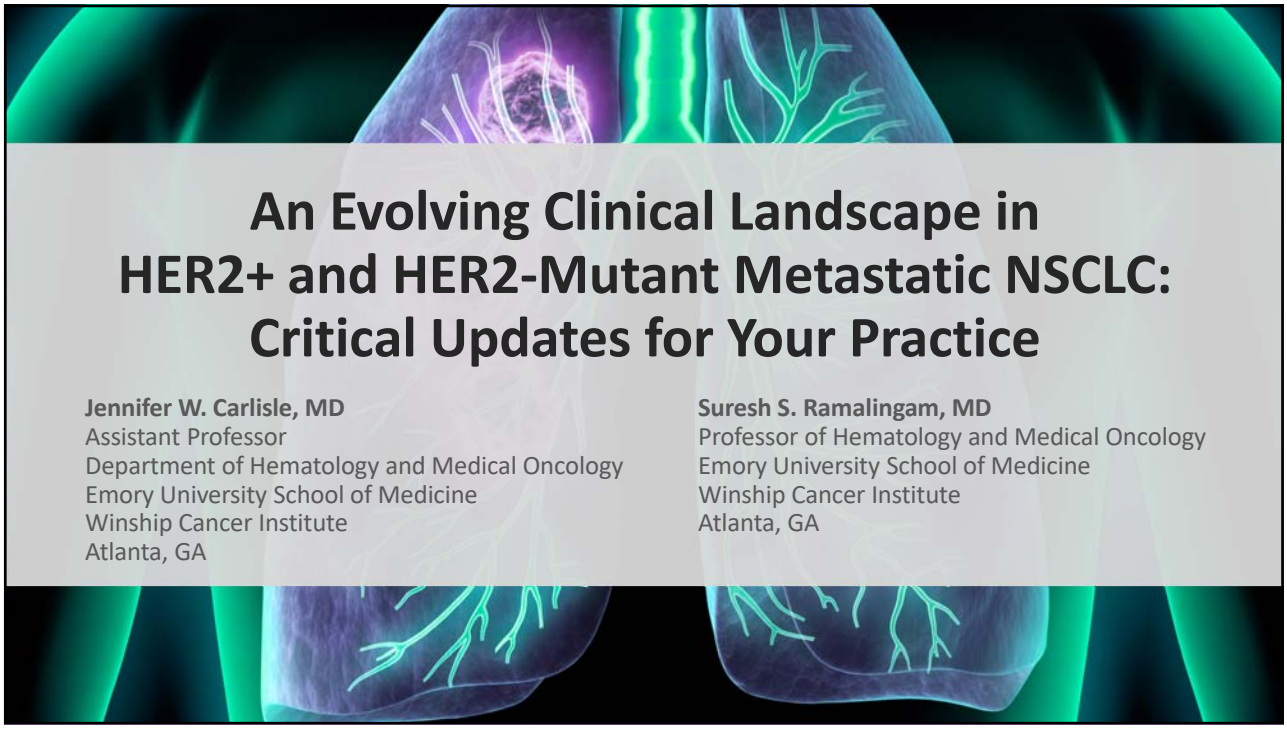

An Evolving Clinical Landscape in HER2+ and HER2-Mutant Metastatic NSCLC: Critical Updates for Your Practice

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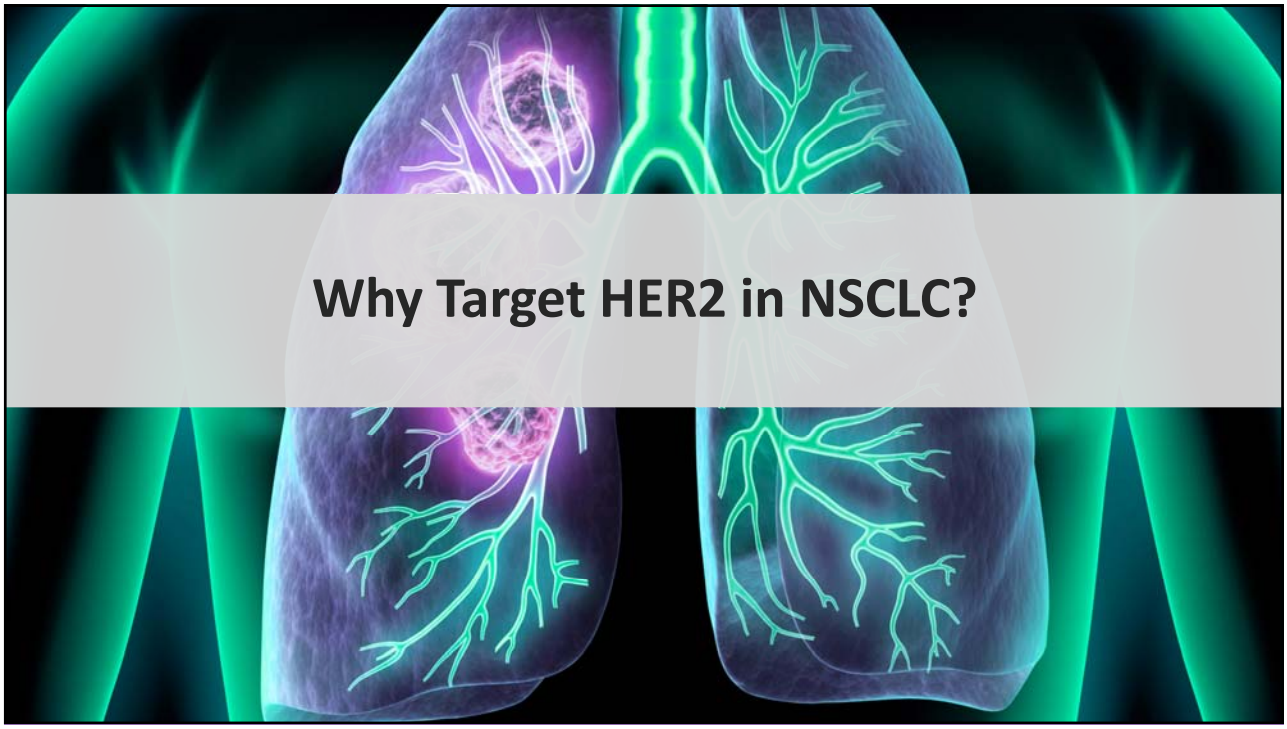
Learning Objectives

Upon completion, participants should be able to:

- Explain the role of HER2 in lung cancer oncogenesis and the novel antibody-drug conjugates in late-stage development for the treatment of HER2-aberrant NSCLC
- Assess clinical safety and efficacy data of HER2-targeted antibody-drug conjugate therapies in NSCLC and identify patients who may benefit from these therapies

Agenda

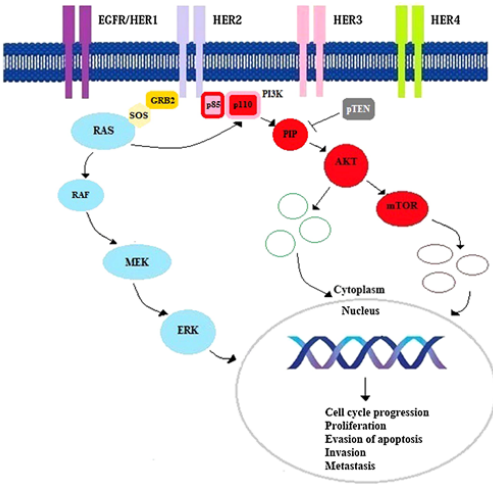
- Why target HER2 in NSCLC?
- What to target: *HER2* mutations, amplifications, and/or overexpression?
- Efficacy of HER2-targeted ADCs in NSCLC
- Safety of HER2-targeted ADCs in NSCLC
- Future directions in the HER2-targeted treatment of lung cancer



Why Target HER2 in NSCLC?

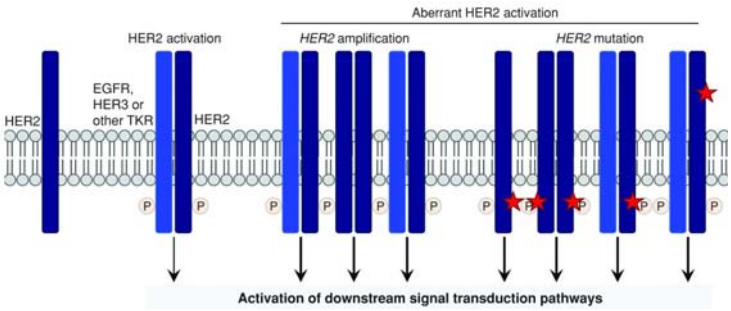
HER2: Human Epidermal Growth Factor Receptor 2

- Member of the ERBB family of tyrosine kinase receptors
- Ligand binding promotes receptor dimerization and auto-phosphorylation of the kinase domain
- Results in the initiation of a variety of signaling pathways including MAPK, PI3K/AKT, PKC, and STAT
- Seen in breast, gastroesophageal, and non–small cell lung cancer



Mar N, et al. *Lung Cancer.* 2015;87:220-5.

HER2 Alterations Promote Cell Growth

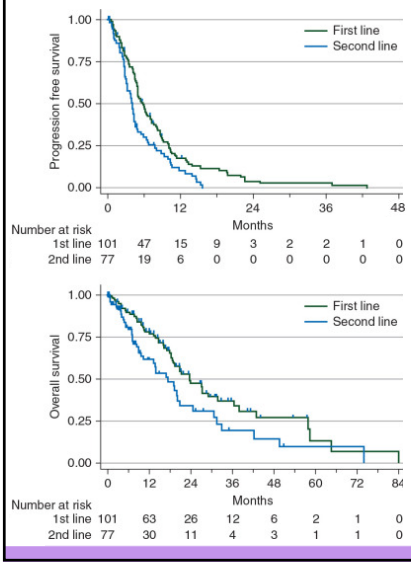


May be a primary oncogenic driver or mechanism of acquired resistance

- Series of 175 patients with no prior targeted therapy:
  - *HER2* amplification was detected by FISH in 5 of 175 cases (3%)
  - *HER2* mutation was detected in 4 of 148 specimens (3%) all in exon 20
- Among 920 patients in the Lung Cancer Mutation Consortium studies:
  - 24 patients (3%) harbored exon 20 insertion mutations (95% confidence interval, 2% to 4%)

Weigelt B, et al. *Cancer Discov.* 2013;3:145-7; Li BT, et al. *J Thorac Oncol.* 2018;11:414-19; Pillai RN, et al. *Cancer.* 2017;123:4099-105.

HER2 Mutations in NSCLC



- Mutations seen in 2% to 4% of NSCLC
  - More common in female never-smokers with adenocarcinoma
- Retrospective study 101 patients with HER2 exon 20 insertion
  - Median OS = 24 months
- Conventional chemotherapy
  - First line: ORR 43.5% and median PFS 6 months (n = 93)
  - Second line: ORR 10% and median PFS 4.3 months (n = 52)
- HER2-targeted therapies: trastuzumab* = 57, neratinib* = 14, afatinib = 9, lapatinib* = 5, T-DM1* = 1
  - ORR was 50.9% and PFS was 4.8 months with trastuzumab or T-DM1

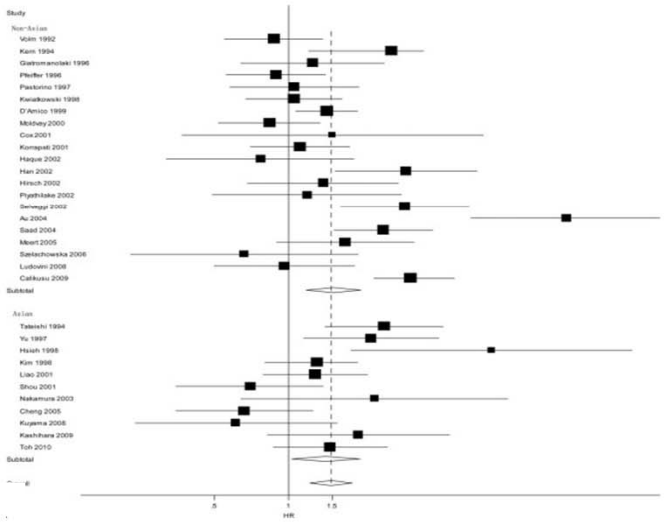
* = off-label use.

Mazières J, et al. *Ann Oncol*. 2016;27:281-6.

HER2 Overexpression in NSCLC

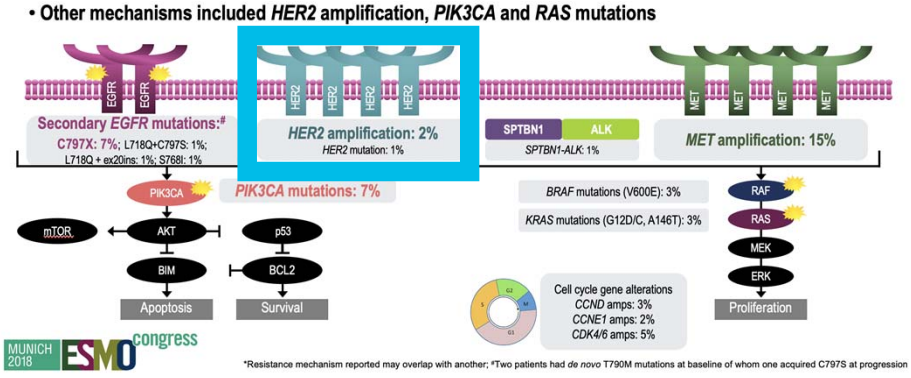
Meta-analysis assessing HER2 by IHC in lung cancer

- Forty studies (6,135 patients) were included
- HER2 overexpression was a marker of poor prognosis
- HR for death was 1.48 (95% CI, 1.22 to 1.80) in NSCLC

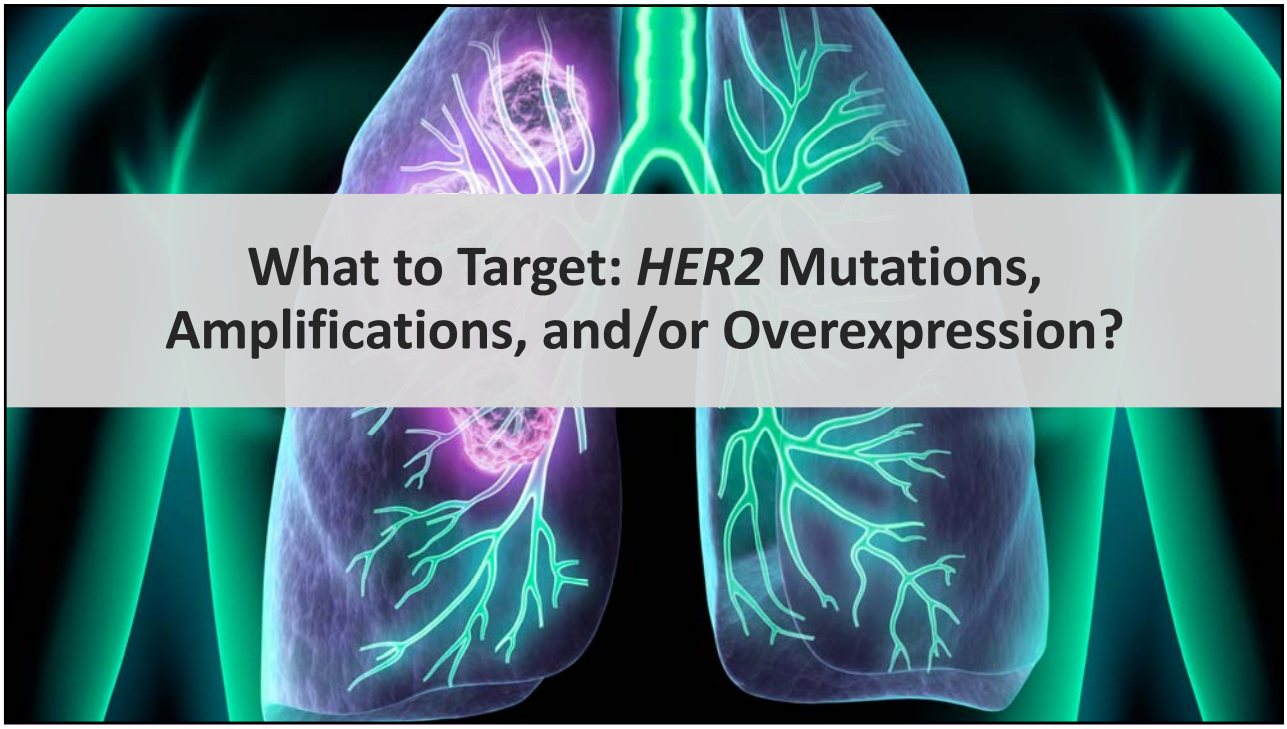


Liu L, et al. *J Thorac Oncol*. 2010;5:1922-32.

HER2 Acquired Resistance Mechanism in EGFR-Mutant NSCLC



Ramalingam S, et al. ESMO 2018. Abstract LBA50.



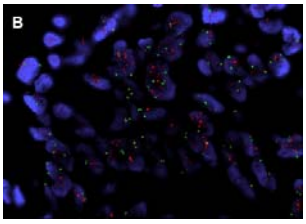
What to Target: *HER2* Mutations, Amplifications, and/or Overexpression?

Defining and Measuring *HER2* Amplification and Overexpression

- No clear consensus definition in lung cancer
- No clear association between amplification and overexpression (unlike breast cancer)

***HER2* gene amplification:**
- **HER2-to-centromere protein (CEP17) ratio of at least 2.0**

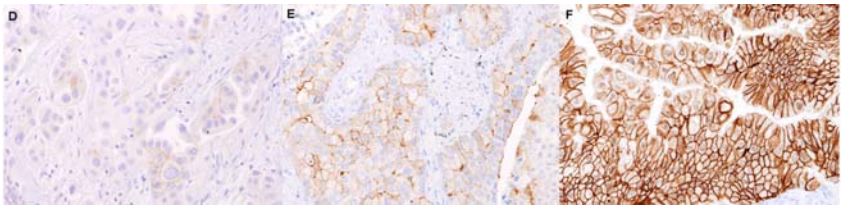
Test: FISH, Dako



(HER2 = red, CEP17 = green)

HER2 protein overexpression:
- **2+ or 3+ on the basis of published methods used for breast cancers**

Test: IHC staining, Ventana probe

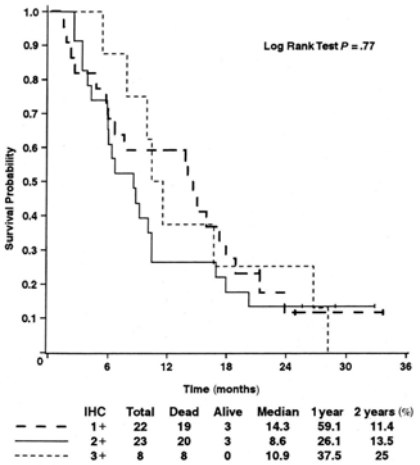


0/1+ **2+** **3+**

Li BT, et al. *J Thorac Oncol*. 2018;11:414-19; Kim EK, et al. *PLoS One*. 2017;12:e0171280.

Trastuzumab +/- Chemotherapy Tested in HER2-Expressed NSCLC

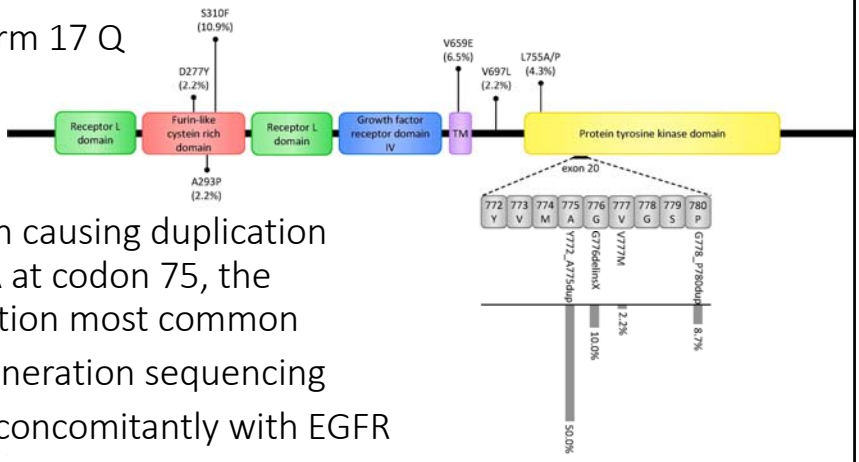
- CALGB phase 2 trial of trastuzumab in 24 patients with 2+ or 3+ HER2 expression had 1 partial response and 1 treatment-related death from pulmonary toxicity (Clamon et al. *Cancer.* 2005;103:1670-5)
- Gemcitabine/cisplatin +/- trastuzumab in 103 patients with 2+ or 3+ HER2 expression was safe, but the addition of trastuzumab did not improve ORR, PFS, or OS (Gatzemeier et al. *Ann Oncol*. 2004;15:19-27)
- ECOG phase 2 trial of carboplatin, paclitaxel, trastuzumab in 53 patients with 1+ to 3+ HER2 expression:
  - ORR: 24.5% (95% CI, 13.8 to 38.3) n = 52
  - Median PFS: 3.3 months
  - Median OS: 10.1 months; 1-year survival rate was 42%



Langer CJ, et al. *J Clin Oncol*. 2004;22:1180-7.

HER2 Mutations in NSCLC

- *HER2* gene on long arm 17 Q
- Most mutations are in exon 20, in the TKI domain
- 12 base-pair insertion causing duplication of amino acids YVMA at codon 75, the Y772_A775dup insertion most common
- Test: RT-PCR, next-generation sequencing
- Have been reported concomitantly with EGFR mutations



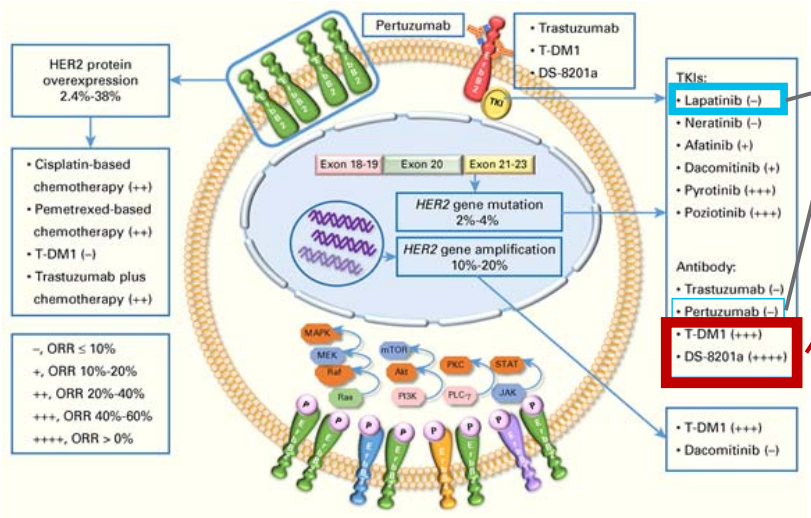
Jebbink M, et al. *Cancer Treat Rev.* 2020;86:101996.

TKIs Studied in HER2-Mutated NSCLC

	Author	Phase (Name)	Drug	No pts	DCR %	ORR %	PFS (months)	OS (months)
2015	*Kris*	II	dacomitinib	26	-	12	3	9
	De Greve	II	afatinib	33	53	-	-	-
	Mazieres	EURHER	afatinib	11	63.7	18.2	3.9	-
	Dziadziusko	NICHE	afatinib	13	53.8	7.7	3.7	13.5
	Peters	NPU	afatinib	28	4/10 >1 yr	-	9.6	-
	Lai	Retrosp	afatinib	23	70	13	-	23
	Fang	Retrosp	afatinib	32	69	1	3.2	-
	Hyman	SUMMIT	neratinib*	26	-	3.8	5.5	-
	Robichaux	II	poziotinib**	12	-	42	5.6	-
2019	*Wang*	II	pyrotinib*	15	73.3	53.3	6.4	12.9

* = off-label use. ** = investigational.
Adapted from Jebbink M, et al. *Cancer Treat Rev.* 2020;86:101996.

Summary of HER2 Alterations and Treatments Tested



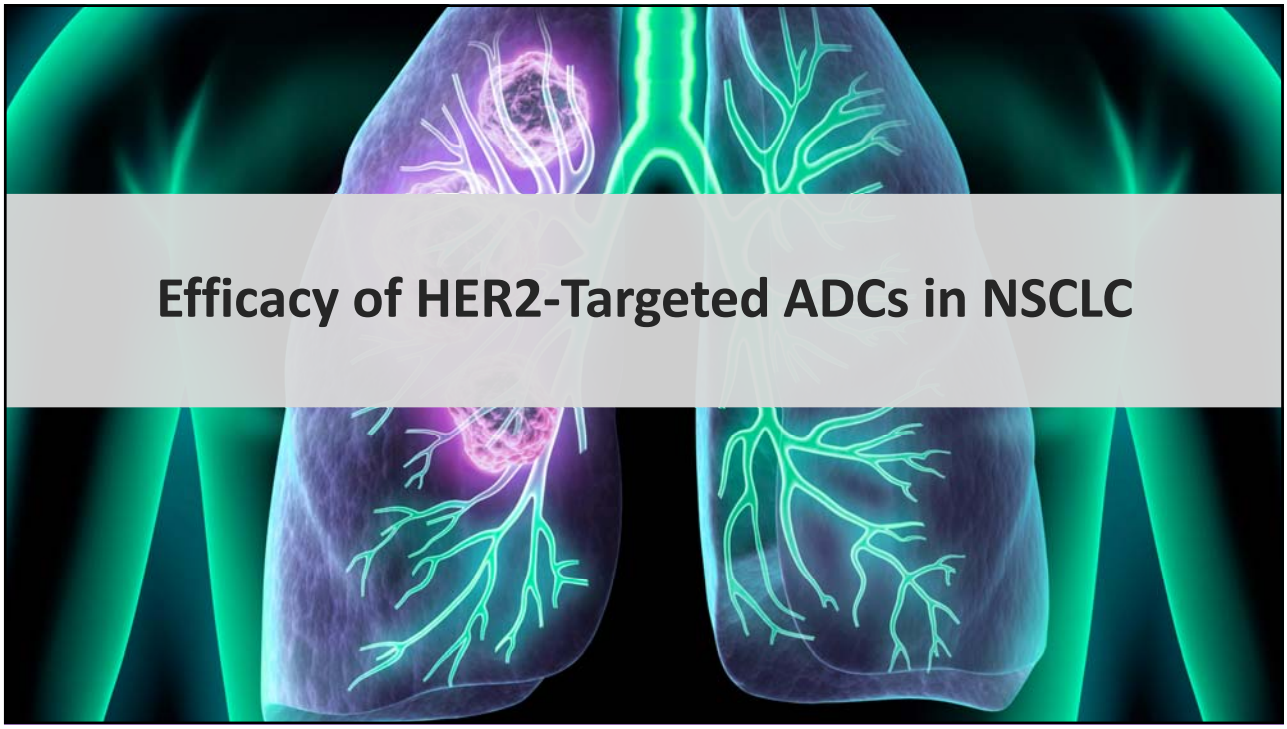
Lapatinib* (dual EGFR/HER2 TKI) and pertuzumab (dimerization inhibitor) have thus far been studied in non-HER2 selected patients with NSCLC with disappointing results**

ADCs:

- **TDM-1*: currently recommended on NCCN guidelines for HER2-mutated NSCLC**
- **DS8201a: Trastuzumab deruxtecan*, new trial results**

* = off-label use. ** = investigational.

Zhao J, et al. *JCO Precision Oncol.* 2020;4:4411-25.



Efficacy of HER2-Targeted ADCs in NSCLC

Efficacy of Ado-Trastuzumab Emtansine

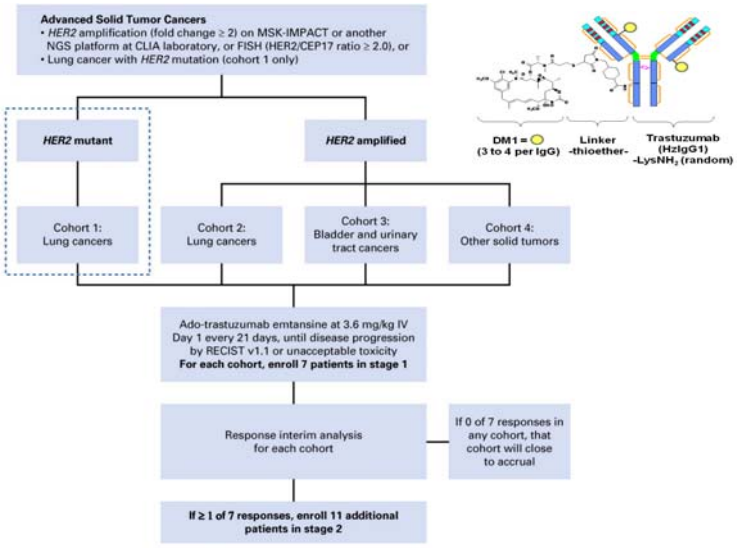
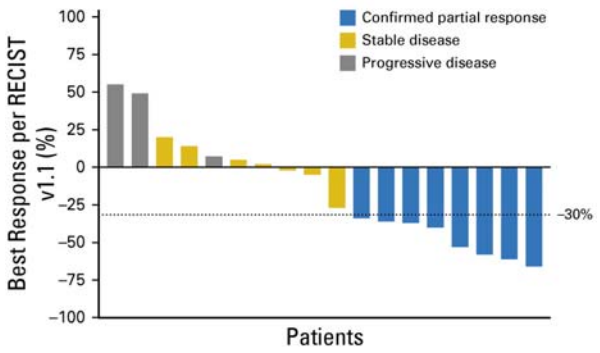


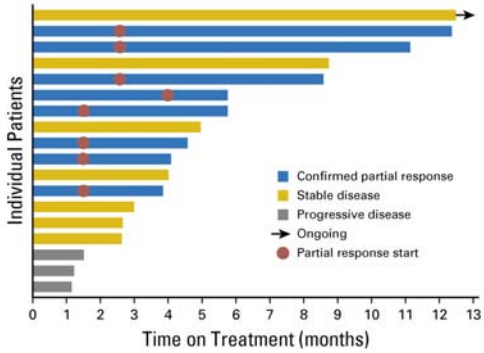
Table 1. Patient Characteristics

Characteristic	No. of Patients (%)
Total patients treated	18 (100)
Median age, years (range)	64 (47-74)
Female	13 (72)
Smoking status	
Former smoker	11 (61)
Never-smoker	7 (39)
Karnofsky performance status	
90%	7 (39)
80%	8 (44)
70%	3 (17)
Histology, adenocarcinoma	18 (100)
Median No. of lines of prior systemic therapy (range)	2 (0-4)
0 prior line	3
1 prior line	5
2 prior lines	4
3 prior lines	3
4 prior lines	3
Prior HER2-targeted therapy	9 (50)
Neratinib	7 (39)
Afatinib	2 (11)
Trastuzumab	2 (11)

Li BT, et al. *J Clin Oncol*. 2018;36:2532-7.

Efficacy of Ado-Trastuzumab Emtansine in NSCLC





- **ORR: 44% (95% CI, 22% to 69%) n = 18**
- **Median PFS: 5 months (95% CI, 3 to 9 months)**
- **Median DOR: 4 months**

- Responses seen in: *HER2* exon 20 insertions and point mutations in the kinase, transmembrane, and extracellular domains
- HER2 immunohistochemistry ranged from 0 to 2+ and did not predict response
- Responders had low HER2 protein expression measured by mass spectrometry

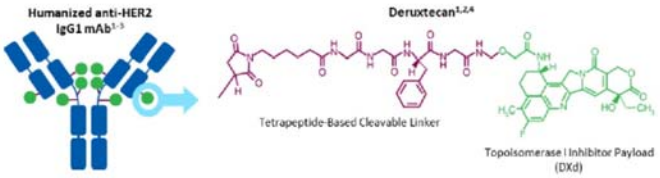
Li BT, et al. *J Clin Oncol*. 2018;36:2532-7.

Trastuzumab Deruxtecan (DS-8201; T-DXd)

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;173-85. 2. Ogitani Y, et al. *Clin Cancer Res*. 2016;22:5097-108. 3. Trial PA, et al. *Pharmacol Ther.* 2018;181:126-42. 4. Ogitani Y, et al. *Cancer Sci.* 2016;107:1039-46.

DESTINY-Lung01 Phase 2 Trial

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

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

Median prior lines of treatment: 2 (range, 1-6)

Prior Treatment, %	Patients (N = 42)
Platinum-based therapy	90.5
Anti–PD-1 or –PD-L1 inhibitor	54.8
Docetaxel	19.0

- 3 patients received prior poziotinib, 2 received afatinib, and 1 received mobocertinib

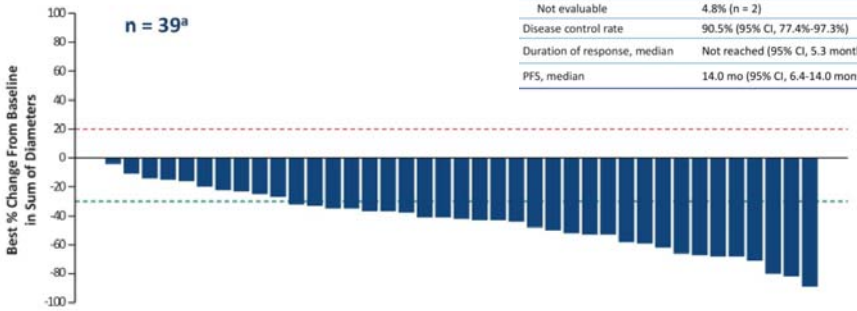
The clinical relevance of these features is under investigation.

Nakada T, et al. *Chem Pharm Bull* (Tokyo). 2019;67:173-85. Ogitani Y, et al. *Clin Cancer Res*. 2016;22:5097-108. 3. Trial PA, et al. *Pharmacol Ther*. 2018;181:126-42. 4. Ogitani Y, et al. *Cancer Sci*. 2016;107:1039-46.

Efficacy of T-DXd

DESTINY-Lung01 HER2-Mutated NSCLC

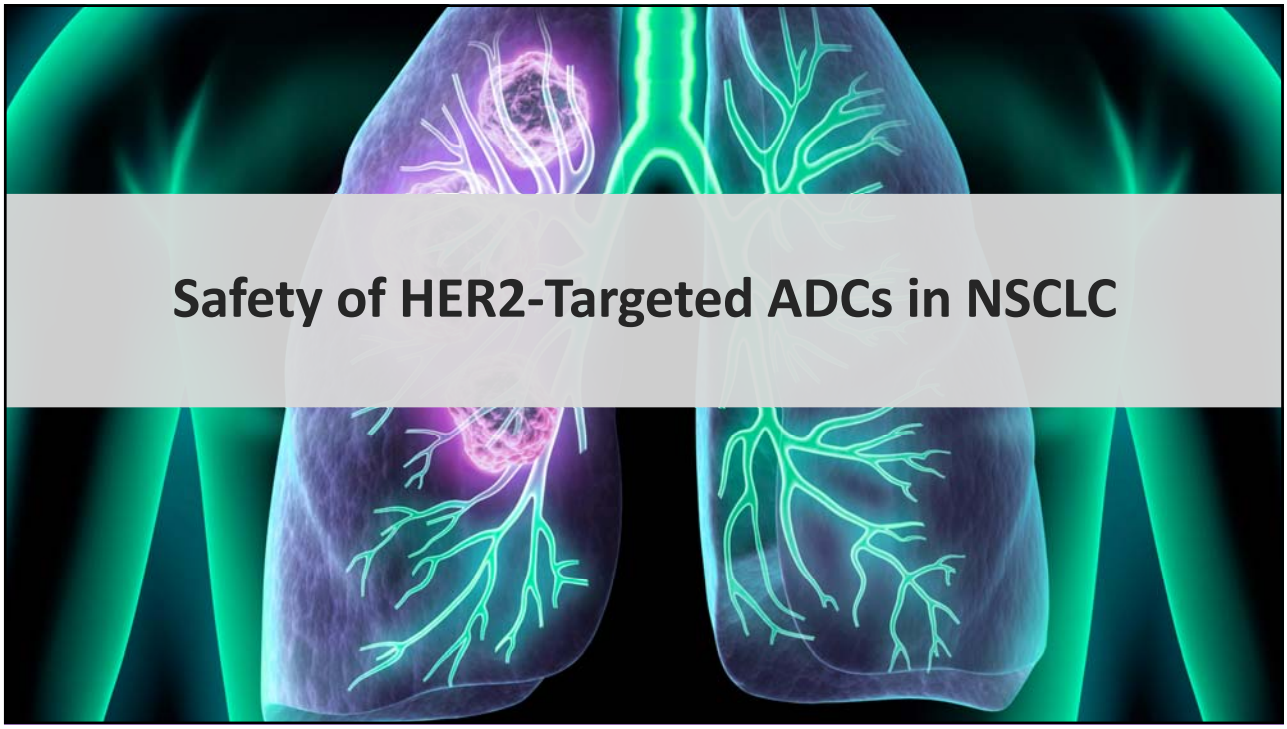
Best Change in Tumor Size



	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)

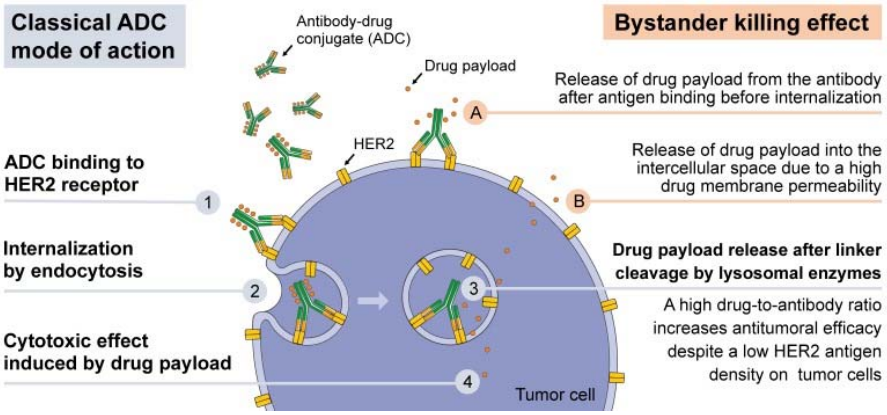
Based on independent central review. Baseline is last measurement taken before enrollment. Shown is best (minimum) percent change from baseline in the sum of diameters for all target lesions.
[a]One patient was missing a baseline assessment and 2 additional patients were missing post-baseline assessments.
The clinical relevance of these features is under investigation.

1. Nakada T, et al. *Chem Pharm Bull* (Tokyo), 2019;67;173-85. 2. Ogitani Y, et al. *Clin Cancer Res*. 2016;22:5097-108. 3. Trial PA, et al. *Pharmacol Ther.* 2018;181:126-42. 4. Ogitani Y, et al. *Cancer Sci.* 2016;107:1039-46.



Safety of HER2-Targeted ADCs in NSCLC

Practical Considerations for Managing HER2 ADCs



- Side effects common to cytotoxic chemotherapy attributable to the payload
- Careful attention to lab parameters, dose delay, and dose reduction

Rinnerthaler G, et al. *Int J Mol Sci.* 2019;20:1115.

Safety of Ado-Trastuzumab Emtansine in Basket Trial

Table 2. Treatment-Related Adverse Events With Total Frequencies of > 10%, According to Common Terminology Criteria for Adverse Events Version 4.1

	No. of Patients (%)			
Adverse Event	Grade 1	Grade 2	Grade 3	Total
Elevated AST or ALT	7 (39)	1 (6)	—	8 (44)
Thrombocytopenia	6 (33)	—	—	6 (33)
Fatigue	5 (28)	1 (6)	—	6 (33)
Infusion reaction	2 (11)	3 (17)	—	5 (28)
Nausea	6 (33)	—	—	6 (33)
Weight loss	1 (6)	2 (11)	—	3 (17)
Rash, maculopapular	3 (17)	—	—	3 (17)
Anorexia	1 (6)	1 (6)	—	2 (11)
Epistaxis	2 (11)	—	—	2 (11)
Anemia	—	1 (6)	1 (6)	2 (11)

NOTE. There were no grade 4 or 5 adverse events.

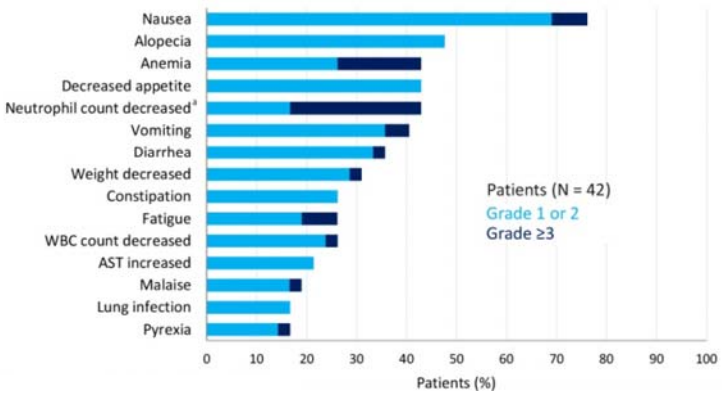
- FDA package insert warnings for ado-trastuzumab emtansine for breast cancer indication
- Hepatotoxicity, liver failure, and death have occurred; monitor hepatic function prior to initiation and prior to each dose
- May lead to reductions in LVEF; assess LVEF prior to initiation

Li BT, et al. *J Clin Oncol.* 2018;36:2532-7.

Safety of T-DXd** in NSCLC

DESTINY-Lung01 HER2-Mutated NSCLC

Treatment-Emergent Adverse Events in >15% of Patients



** = off-label use.

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

Unpublished data from Prof. Egbert F. Smit; Netherlands Cancer Institute; e.smit@nki.nl.

Safety of T-DXd** in NSCLC

DESTINY-Lung01 HER2-Mutated NSCLC

Overall Safety Summary

Type of Adverse Event, n (%)[a]	Patients (N = 42)
Any TEAE	42 (100)
Drug-related	42 (100)
TEAE grade ≥ 3	27 (64.3)
Drug-related	22 (52.4)
Serious TEAE	14 (33.3)
Drug-related	7 (16.7)
Dose adjustments	
TEAE associated with discontinuation[b]	10 (23.8)
Drug-related	8 (19.0)
TEAE associated with dose reduction	16 (38.1)
Drug-related	16 (38.1)
TEAE associated with dose interruption	25 (59.5)
Drug-related	20 (47.6)

- Median treatment duration was 7.76 months (range, 0.7-14.3 months)
- The most common TEAEs associated with dose reduction were fatigue (11.9%) and nausea (9.5%)[c]
- The most common TEAEs associated with dose interruption were decreased neutrophil count (19.0%) and lung infection (7.1%)[c]
- There were 5 patients with TEAEs associated with death[d]; none were related to treatment

[a]Relationship to study drug was determined by the treating investigator.
[b]Each of the following TEAEs were associated with treatment discontinuation: pneumonitis (n = 4), delirium, ILD, diarrhea, disease progression, ejection fraction decreased, weight decreased (n = 1 each). [c]TEAEs occurring in > 2 patients are listed. [d]Each of the following TEAEs were associated with a fatal outcome: seizure, delirium, disease progression (n = 2), and pneumonia (fungal).

** =off-label use.
Unpublished data from Prof. Egbert F. Smit; Netherlands Cancer Institute; e.smit@nki.nl.

Safety of T-DXd** in NSCLC

DESTINY-Lung01 HER2-Mutated NSCLC

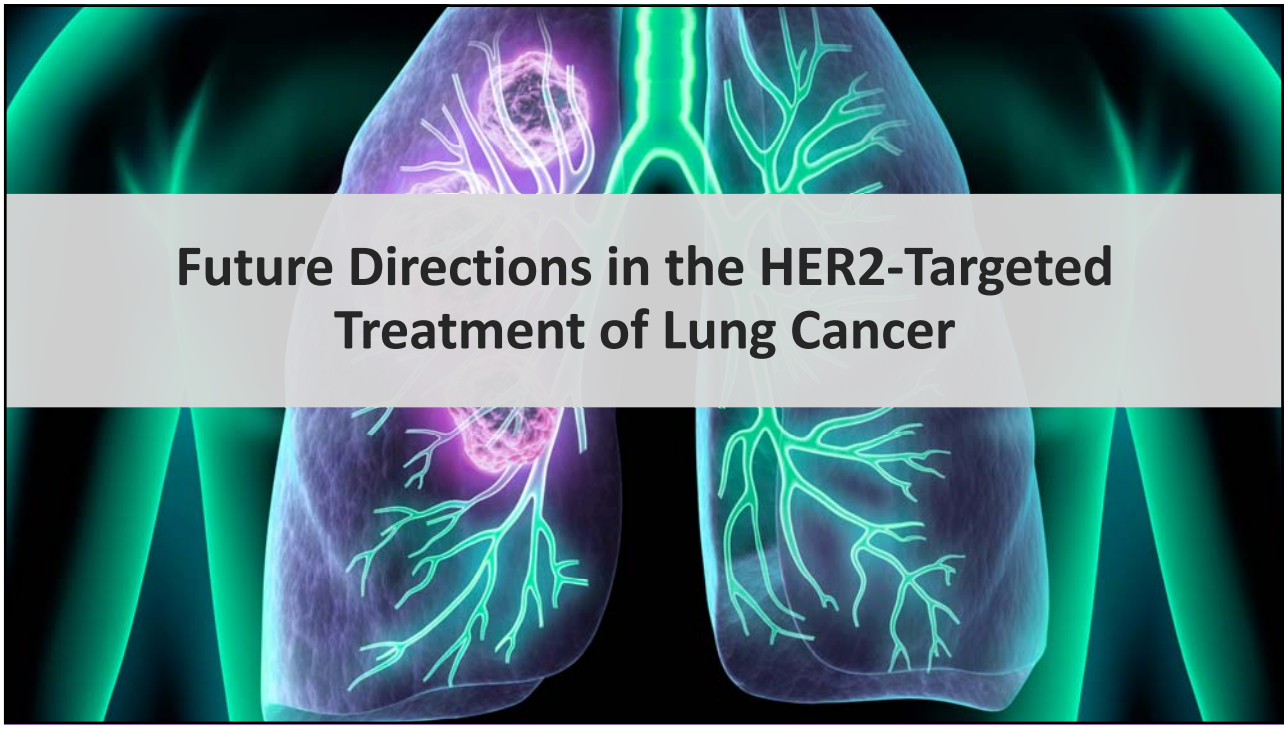
AEs of Special Interest: Interstitial Lung Disease (ILD)

	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

** = off-label use
Drug-related; ILD was determined by an independent ILD Adjudication committee based on 44 preferred terms.
1 case of potential grade 1 ILD was pending adjudication.

Unpublished data from Prof. Egbert F. Smit; Netherlands Cancer Institute; e.smit!nki.nl.



Future Directions in the HER2-Targeted Treatment of Lung Cancer

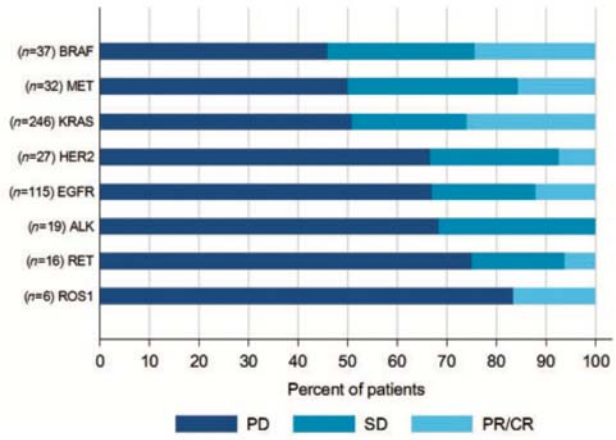
Key Questions

- Role of immunotherapy in HER2-mutated NSCLC
- Optimal setting for HER2-targeted agents in metastatic NSCLC
- Role of HER2-targeted agents in HER2-amplified NSCLC
- Management of early stage NSCLC with HER2 mutation

Combination Approaches Based on DS-8201

- Monotherapy with the investigational product DS-8201 has yielded promising results
- Can this be combined with platinum-based chemotherapy?
- Combinations with other rational targeted agents?
- Identification of patients at high-risk of poor outcomes will guide more-aggressive treatment approaches

Role of Checkpoint Inhibition in NSCLC Patients With Oncogenic Mutations



- Low response rate with single-agent IO therapy
- What is the role of chemo + IO?
- How can the efficacy of immunotherapy be improved in HER2-mutated NSCLC?

Mazieres J, et al. *Ann Oncol.* 2019;30:1321-8.

Optimal Setting for HER2-Targeted Agents

- Combination chemotherapy remains the standard of care
  - Response rate ~ 40%
  - Median PFS ~ 5 to 6 months
- An efficacy profile comparable or better than chemotherapy will be required for first-line therapy for HER2-targeted agents
- DS-8201 demonstrated RR > 60% and mPFS ~ 14 months
  - These data position this agent well for first-line use, pending mature data from ongoing trial

Can Targeted Agents Be Used in HER2-Amplified NSCLC?

- HER2 amplification is a common event in NSCLC
- DS-8201 is used for HER2-amplified breast cancer
- Role in NSCLC needs to be evaluated in clinical trials
- Will efficacy be comparable to that seen in HER2-mutated NSCLC?

Role in Early Stage NSCLC

- ADAURA study demonstrated efficacy with osimertinib in early stage NSCLC
- Can HER2-targeted agents benefit patients with early stage disease?
- Given the rarity of HER2 mutation, randomized trials are unlikely to be done in a timely manner
- Similar question for other rare oncogenic events
- Novel trial designs such as neoadjuvant approach may yield insights

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Thank you for participating.