TARGETING HER2 IN NSCLC

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Conquering Thoracic Cancers Worldwide

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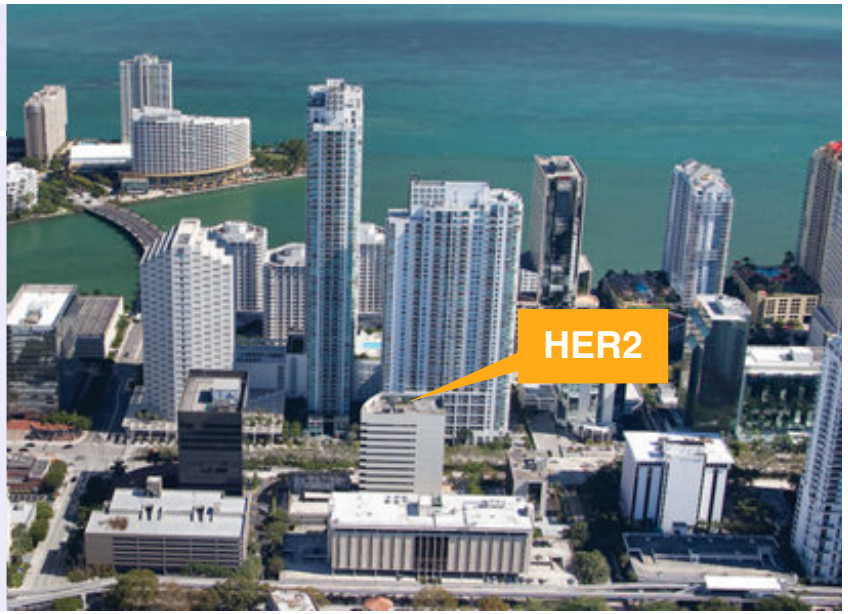
Lung Cancer: Then and Now

When I completed fellowship

- Chemo+/- Bevacizumab
- Erlotinib
- Hospice

Today

- ChemoImmuno
- Immunotx
- Targeted Therapies:
  - EGFR
  - ALK
  - ROS
  - BRAF V600E
  - Met Ex 14 Skip
  - RET
  - KRASG12C
  - ERBB2
  - NTRK

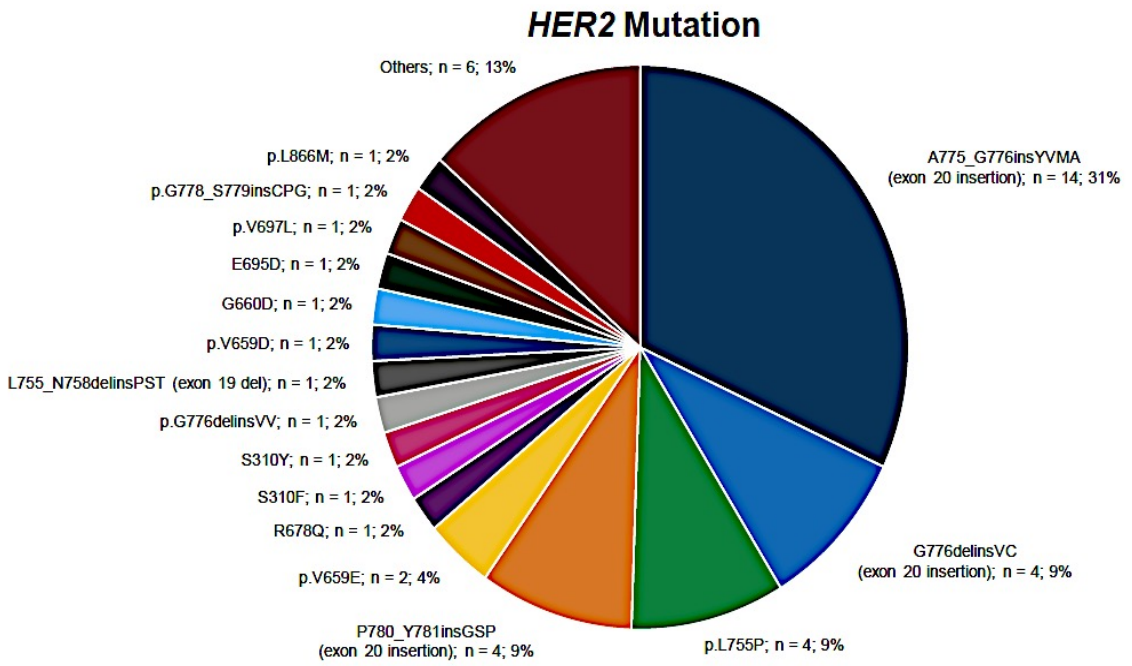


Brickell Avenue, Miami

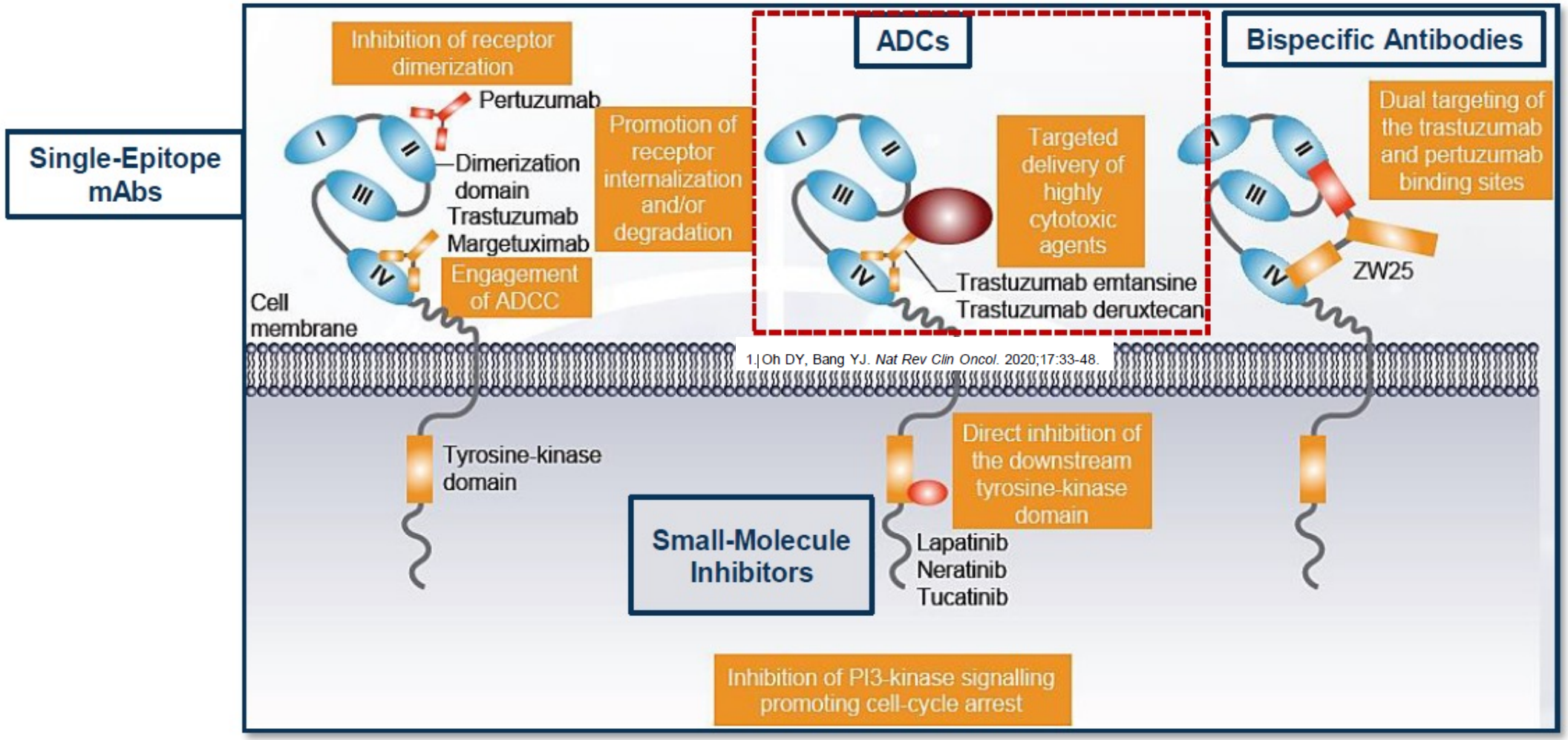
$60/sqft→ $666/sqft

HER2 + Lung Cancer

- Approximately 1-3% of NSCLCs have *HER2* mutations
  - Associated with younger age, female, never smoking, poor prognosis, increased brain metastases
  - Seen in adenocarcinoma and squamous cell cancers
- Most common ERBB2 mutation: Exon 20 ins (YVMA variant ~85%)
- Previous case series have suggested clinical tumor responses using anti-ERBB2 small molecules and antibody therapies.



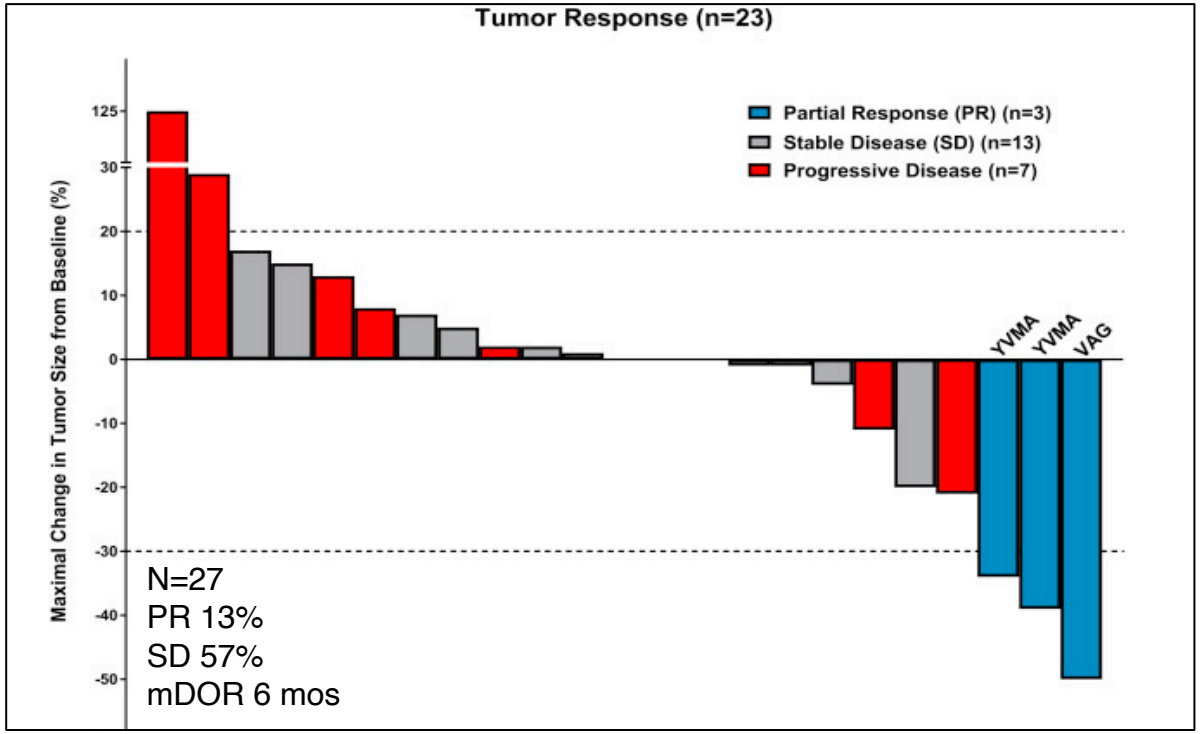
Mechanism of Action of HER2 Targeted Therapies



Oh DY, Ban YJ. Nat Rev Clin Oncol, 2020

HER2 Mutated Lung Cancer : Therapeutic Approaches

Afatinib



Ado-Trastuzumab Emtansine

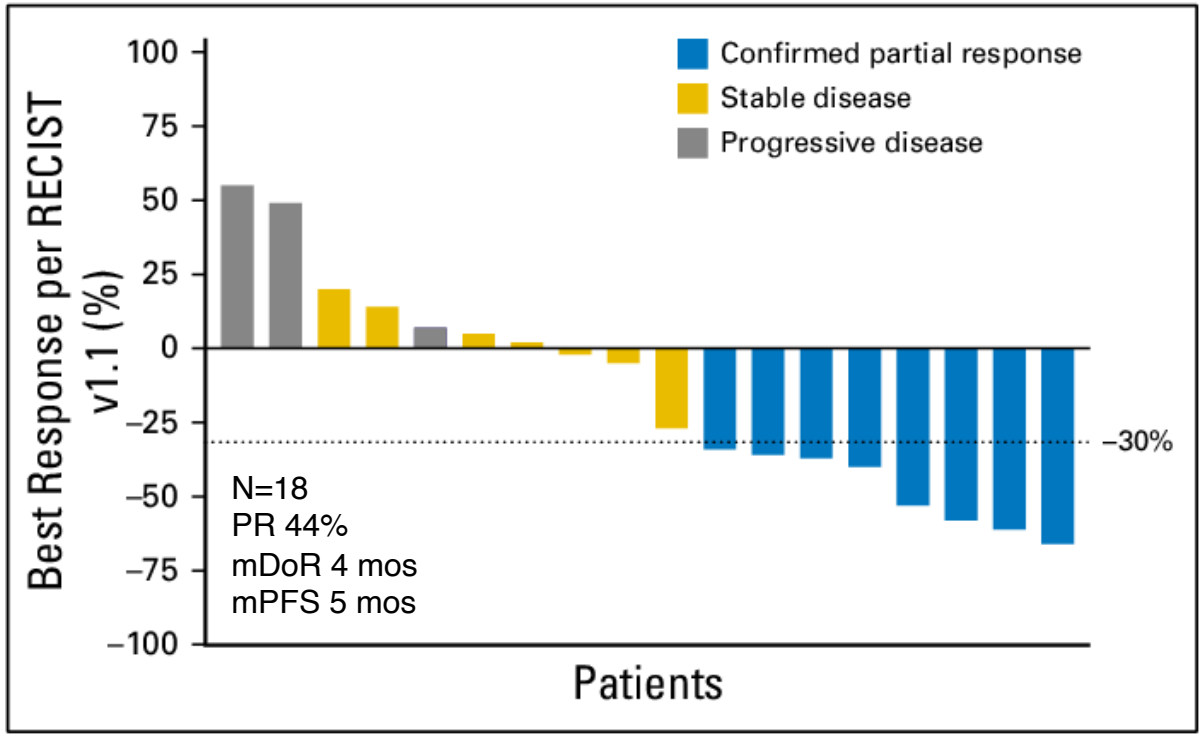


Fig 1. Waterfall plot of best response. RECIST, Response Evaluation Criteria in Solid Tumors.

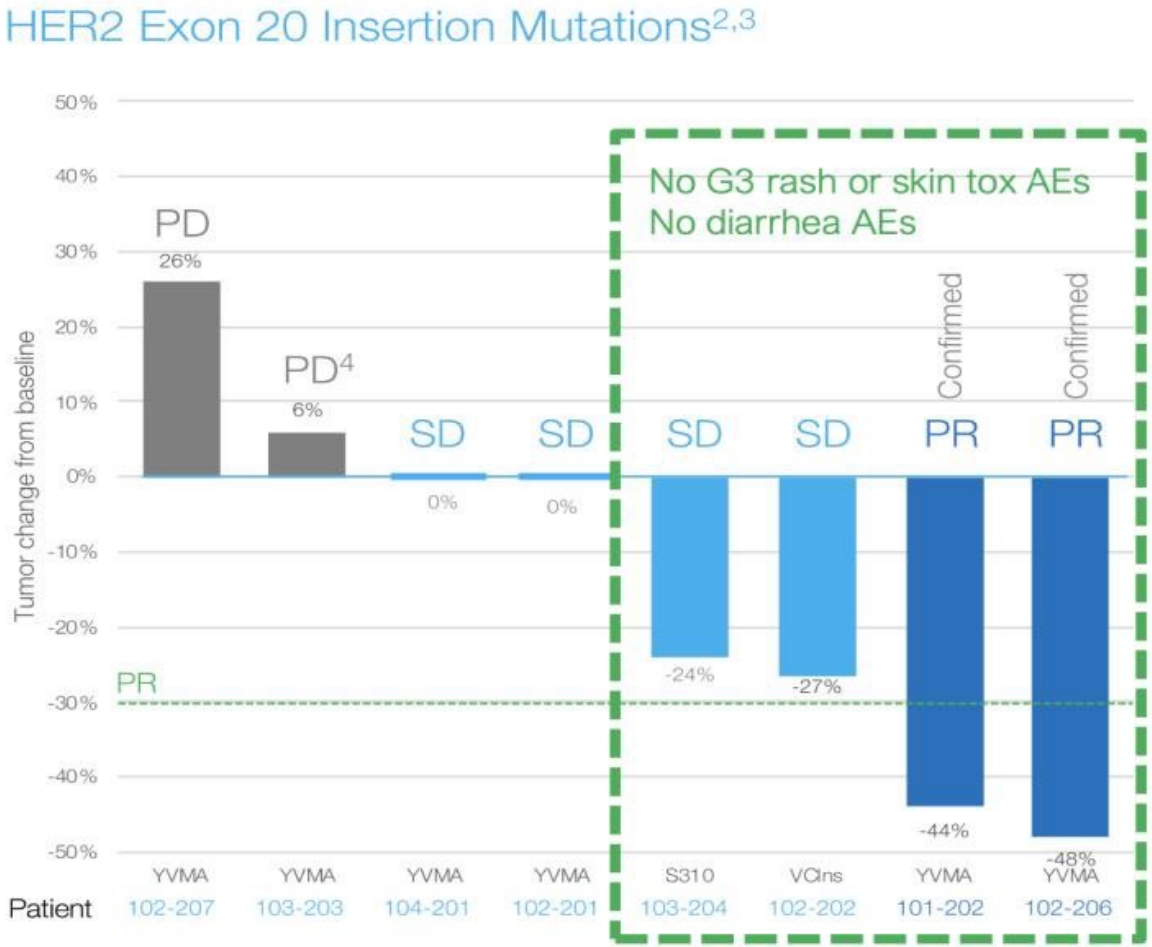
1. Lai WV, et al Afatinib in patients with metastatic or recurrent HER2-mutant lung cancers: a retrospective international multicentre study. Eur J Cancer. 2019 Mar;109:28-35.
2. Li BT, et al. Ado-Trastuzumab Emtansine for Patients With HER2-Mutant Lung Cancers: Results From a Phase II Basket Trial. J Clin Oncol. 2018 Aug 20;36(24):2532-2537.

HER2 Tyrosine Kinase Inhibitors in NSCLC

Drug	Sample size (N)	ORR (%)	mPFS	Toxicities
Afatinib[1]	28	19%	3 mos	Diarrhea (95%), rash/ acne (80%), stomatitis
Afatinib[2]	13	8%	16 weeks	Rash, diarrhea, vomiting
Dacomitinib[3]	26	12%	3 mos	Diarrhea (90%), dermatitis (73%), fatigue (57%)
Neratinib[4]	26	3.8%	5.5 mos	Diarrhea (73.8%), nausea (43.3%), vomiting (41.1%)
Mobocertinib[5]	5	20%		Diarrhea (83%), Anorexia (50%)
Poziotinib[6]	90	27.8%	5.5 mos	Grade 3: Rash (29%) Diarrhea (26%) Stomatitis (10%)-87% dose reductions 14% discontinuation
Poziotinib[7]	48 (First Line)	44%	5.6 mos	92% Diarrhea; 30% Creatinine Clearance
Pyrotinib[8]	60	30%	6.9 mos	Diarrhea (91.7%) Elevated blood creatinine (28.3%) Vomiting (28.3%) LFTs (30%)
Tarloxotinib[9]	9	22%	--	QT prolongation (60.9%) Rash (43.5%) Diarrhea (21.7%) Nausea (21.7%)

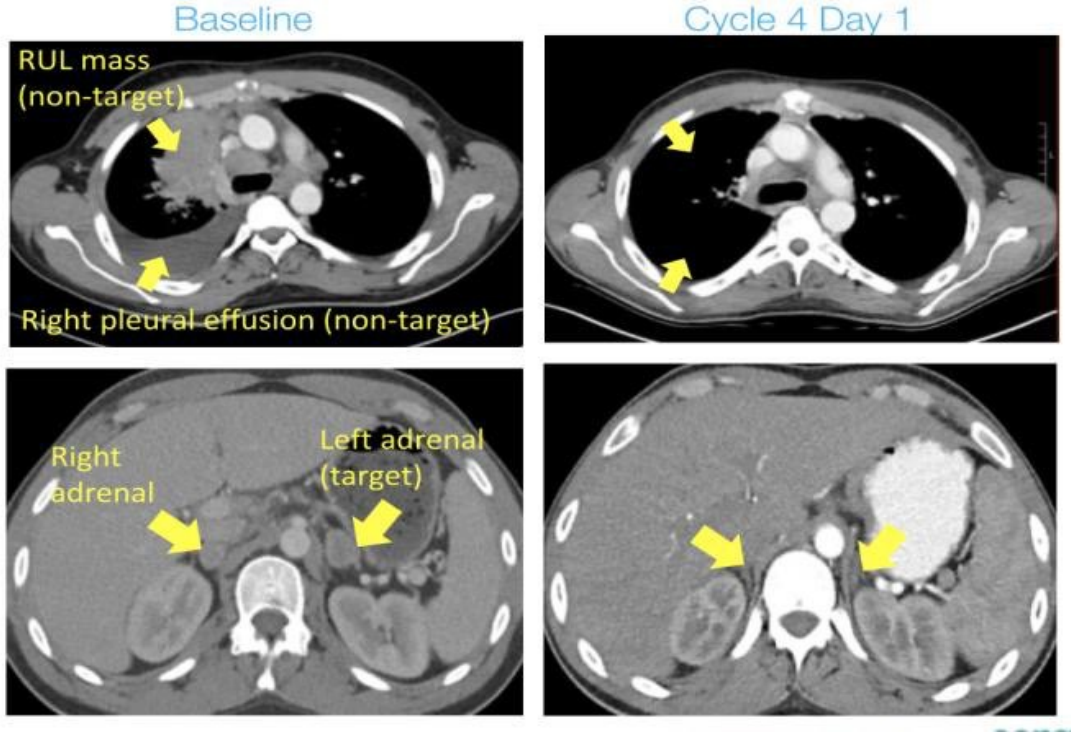
1. Peters et al. JTO 2018; 2. Dziadziuzko et al. JTO 2019, 3. Kris et al. Ann Oncol 2015, 4. Hyman et al. Nature 2018, 5. Zhou C JCO 2020,
6. Cornelissen et al. WCLC 2020, 7. Zhou C JCO 2020, 8. Zhou C et al JCO 2020, 9. Liu et al. ESMO 2020

Tarloxotinib in Patients with NSCLC EGFR/HER2 Exon 20 Ins Mutations: RAIN-701



Cohort B

	% (n)
ORR	22% (2/9)
DCR	67% (6/9)



Liu ESMO 2020

Trastuzumab-Deruxtecan-DESTINY-Lung01

Antibody Drug Conjugate

8/11/2022
1st FDA Approved HER2 Agent

- Unresectable/metastatic nonsquamous NSCLC
- Relapsed/refractory to standard treatment
- Measurable disease by RECIST v1.1
- Asymptomatic CNS metastases at baseline[a]
- ECOG PS 0 or 1
- Locally reported *HER2* mutation (cohort 2)[b]

Cohort 1[c] (n = 49)
HER2 overexpressing
(IHC 3+ or IHC 2+)
T-DXd 6.4 mg/kg Q3W

Cohort 1a[c] (n = 41)
HER2 overexpressing
(IHC 3+ or IHC 2+)
T-DXd 5.4 mg/kg Q3W

Cohort 2 (n = 42)
***HER2* mutated**
T-DXd 6.4 mg/kg Q3W

Cohort 2 (n = 49)
***HER2* mutated**
T-DXd 6.4 mg/kg Q3W

- **Primary endpoint:** Confirmed ORR by ICR[d]
- **Secondary endpoints:** DOR, PFS, OS, DCR, and safety
- **Exploratory endpoint:** biomarkers of response

Data cutoff: May 3, 2021
- 91 pts with *HER2*mut NSCLC
- 15 pts (16.5%) remain on treatment
- 76 pts (83.5%) discontinued, primarily for PD and AEs

Li. ESMO 2021. Abstr LBA45. LI. NEJM. 2022.

HER2-Mutated NSCLC Cohort in DESTINY-Lung01: Baseline Characteristics

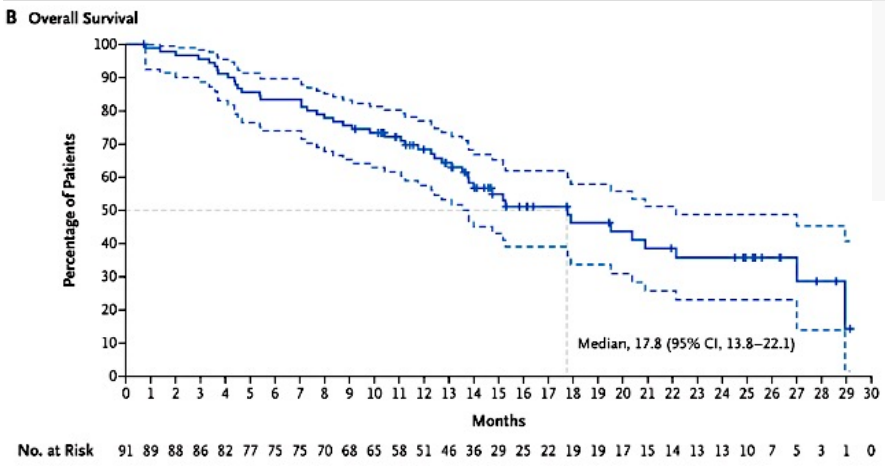
Parameter	T-DXd (N = 91)
Median age, yr (range)	60.0 (29.0-88.0)
Female, %	65.9
Race, %	
• White	44.0
• Asian	34.1
• Black	1.1
• Other	20.9
ECOG PS 1, %	74.7
HER2 mutation, %	
• Kinase domain	93.4
• Extracellular domain	6.6
Asymptomatic CNS mets, %	36.3

Parameter	T-DXd (N = 91)
Smoking status, %	
• Never	57.1
• Former	40.7
• Current	2.2
History of prior lung resection, %	22.0
Prior systemic cancer therapy, %	98.9
Median prior lines therapy, n (range)	2 (0-7)
Prior treatment, %	
• Platinum-based therapy	94.5
• Anti–PD-(L)1 therapy	65.9
• Platinum-based and anti–PD(L)1	62.6
• Docetaxel	19.8
• HER2 TKI	14.3

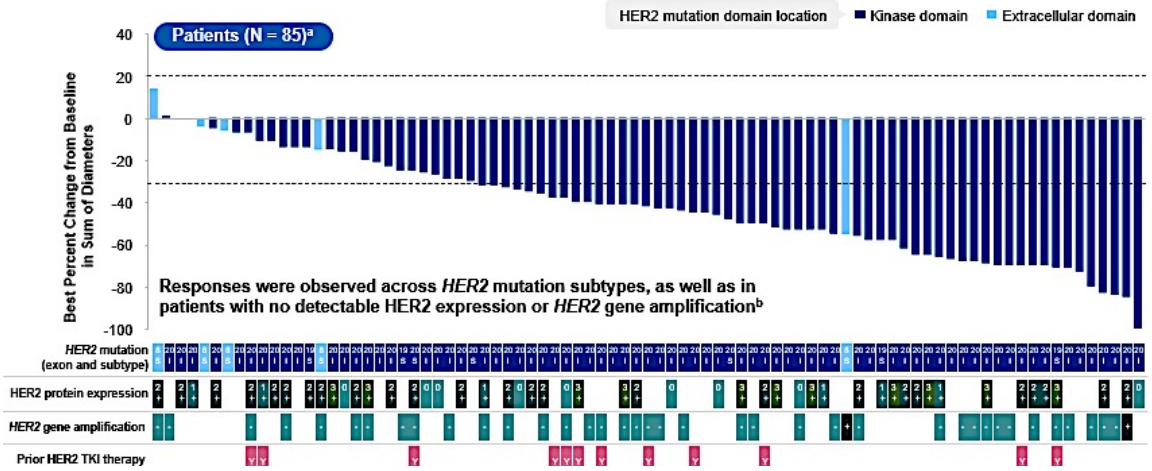
Li. ESMO 2021. Abstr LBA45. LI. NEJM. 2022.

HER2-Mutated NSCLC Cohort in DESTINY-Lung01: Efficacy

Outcome	T-DXd (N = 91)
Confirmed ORR, n (%)	50 (54.9)
• CR	1 (1.1)
• PR	49 (53.8)
• SD	34 (37.4)
• PD	3 (3.3)
• NE	4 (4.4)
ORR by subgroup, n/N (%)	49/85 (57.6)
• HER2 kinase domain mutation	46/86 (53.5)
• Prior platinum-based therapy	37/57 (64.9)
• Prior platinum-based therapy and anti–PD-(L)1	18/33 (54.5)
• BL asymptomatic CNS metastases	
• No BL asymptomatic CNS metastases	32/58 (55.2)
DCR, n (%)	84 (92.3)
Median DoR, mo (95% CI)	9.3 (5.7-14.7)
Median PFS, mo (95% CI)	8.2 (6.0-11.9)
Median follow-up, mo (range)	13.1 (0.7-29.1)



ORR 55%
DoR 9.3 mos
PFS 8.2 mos
OS 17.8mos



Li. ESMO 2021. Abstr LBA45. LI. NEJM. 2022.

HER2-Mutated NSCLC Cohort in DESTINY-Lung01: Safety

Drug-Related TEAEs Reported in ≥20% of Patients, n (%)	T-DXd (N = 91)	
	Any Grade	Grade ≥3
Nausea	66 (72.5)	8 (8.8)
Fatigue	48 (52.7)	6 (6.6)
Alopecia	42 (46.2)	0
Vomiting	36 (39.6)	3 (3.3)
Neutropenia	32 (35.2)	17 (18.7)
Anemia	30 (33.0)	9 (9.9)
Diarrhea	29 (31.9)	3 (3.3)
Deceased appetite	27 (29.7)	0
Leukopenia	21 (23.1)	4 (4.4)
Constipation	20 (22.0)	0

- **TRAEs Discontinuation: 25%**
- **Drug-related TRAEs associated with discontinuation:**
  - Pneumonitis (13.2%); ILD (5.5%)
- **Most common drug-related TRAEs associated with dose reduction:**
  - Nausea (11.0%); Fatigue (8.8%)
- **Drug-related ILD/pneumonitis** -24 pts (26.4%)-Grade 1/2: 18 (19.8%)
  - Median time to onset: 141 days (range: 14-462)
  - Median duration: 43 days , 54% of cases fully resolved

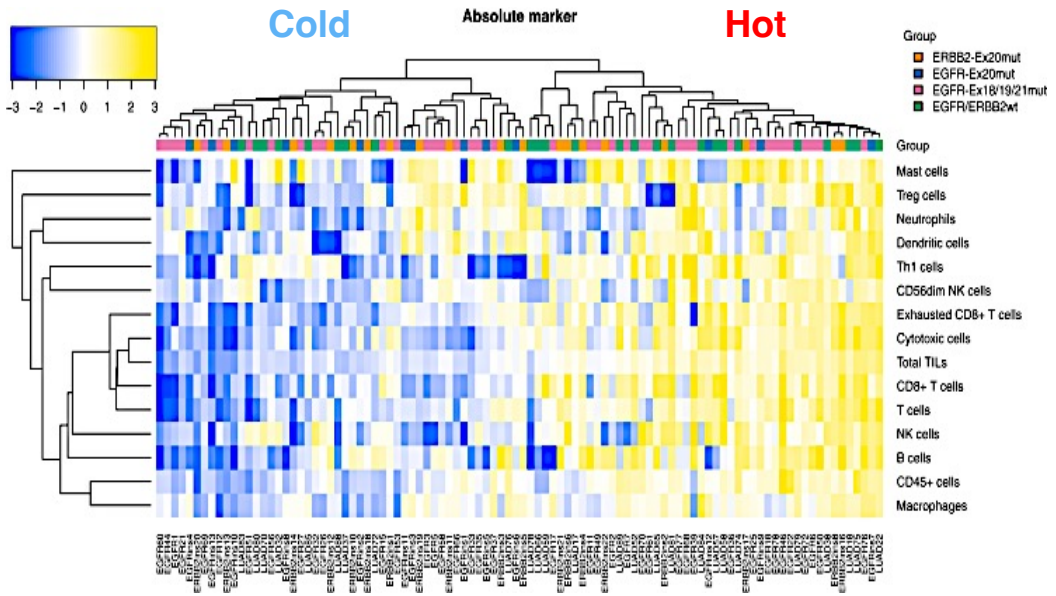
Li. ESMO 2021. Abstr LBA45.

Efficacy of Immune Checkpoint Inhibitors in HER2+ NSCLC

Retrospective Series

Study	Sample size (N)	ICI used	PDL1 >1%	ORR (%)	mPFS (mos)	mOS (mos)
MSKCC[1]	26	N/A	23%	12%	1.9	10.4
IMMUNOTARGET[2]	29	Nivolumab 89% >2 lines 95%	53.3%	7.4%	2.5	20.3
MD Anderson[3]	16	--	--	6%	1.8	17.1
French Lung Cancer Registry[4]	23	Nivolumab 83% >2 lines 100%	5.5 mos	27.3%	2.2	20.4

Clustering of ERBB2 tumors by Immune Microenvironment



Kirchner, ESMO Open 2021 Oct;6(5)

1. Lai et al. ASCO 2018; 2. Mazieres et al. Ann Oncol 2019, 3. Negrao et al. ASCO 2018 , 4. Guisier et al. JTO 2020

Moving HER2 Therapy to First Line: DESTINY-Lung03

A phase 1b, multicenter, open-label, dose-escalation trial of T-DXd and durvalumab with chemotherapy in patients with HER2-overexpressing advanced or metastatic NSCLC (North America, Europe, Asia, Australia)

Study Design

Patient Population

- Unresectable, locally advanced, Metastatic HER-overexpressing nonsquamous NSCLC
- Part 1: Disease progression after 1-2 lines of therapy in metastatic setting
- **Part 2: Treatment-naïve for noncurative treatment (N= 136)**
- ECOG 0-1

ClinicalTrials.gov Identifier: NCT04686305

Part 1: Dose-Escalation and Monotherapy Arm

- Arm 1A: T-DXd + durvalumab + cisplatin
- Arm 1B: T-DXd + durvalumab + carboplatin
- Arm 1C: T-DXd + durvalumab + pemetrexed
- Arm 1D: T-DXd

↓

Dose-Expansion Phase

- Arm 2A: T-DXd + durvalumab + cisplatin
- Arm 2B: T-DXd + durvalumab + carboplatin
- Arm 2C: T-DXd + durvalumab + pemetrexed
- Arm 2D: T-DXd + durvalumab

Primary Endpoint

- Safety

Secondary Endpoints

- Confirmed ORR
- DOR
- DCR
- PFS
- OS
- Safety
- Pharmacokinetics
- Immunogenicity

Planchard et al. AACR 2022

Moving HER2 Therapy to First Line: DESTINY-Lung04

Phase 3 study of T-DXd as 1L treatment of NSCLC harboring *HER2* exon 19 or 20 mutations

- Metastatic or unresectable nonsquamous NSCLC
- Treatment naïve for advanced disease
- *HER2*mut exon 19/20 by central or local test
- RECIST v1.1 evaluable

1:1

R

N = 264

T-DXd 5.4 mg/kg Q3W

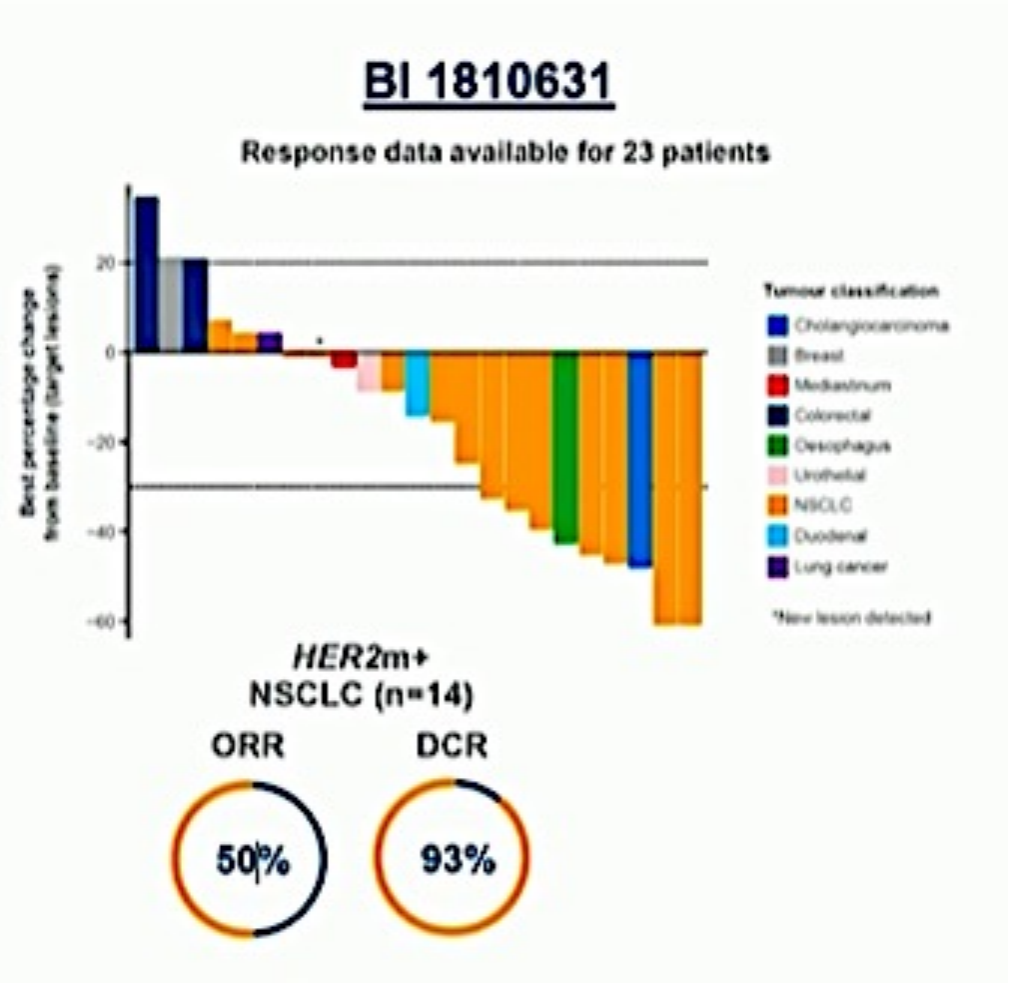
Pembrolizumab + platinum + pemetrexed

- **Primary endpoint:** PFS by BICR
- Prespecified subgroups include *HER2* co-amplification; PD-L1 status (≥1%)

Study Start: October 2021; Study Completion: March 2025
ClinicalTrials.gov Identifier: NCT05048797

The Next Generation of HER2 TKIs:

- Prior TKIs with HER2 activity have been limited by toxicities related to their EGFR inhibition
- Novel HER2-selective TKIs (without activity against other HER/ERBB family members) may lead to enhanced activity and safety
- Several selective HER2 TKIs are now entering clinical development
  - ENLV-002
  - BI 1810631



Ondam et al. AACR NCI EORTC 2022

HER2-Mutated NSCLC : Conclusions

T-DXd is the first FDA approved therapy for HER2-mutated NSCLC in the second-line and later setting: ORR 55% DoR 9.3 mos, OS 17.8mos

TKIs such as poziotinib and pyrotinib have shown promising activity (ORR 38-44%) but with significant toxicity; Novel HER2-selective TKIs may lead to enhanced activity and safety.

Immunotherapy monotherapy has limited activity in HER2 driven NSCLC

Shift from monotherapies to combinations of drugs with different mechanisms (ADC+ICI or TKIs) is already in horizon