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The Role of Antibody Drug Conjugates in Advanced Non-Small Cell Lung Cancer: Guidance for Today and the Path Forward

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CME for MIPS
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Learning Objective 1

Apply molecular testing to identify predictive biomarkers for targeted therapy in advanced NSCLC.

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Learning Objective 2

Evaluate rationale for emerging therapies in advanced or metastatic NSCLC.

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Learning Objective 3

Employ best practices to manage lung cancer during the COVID-19 pandemic.

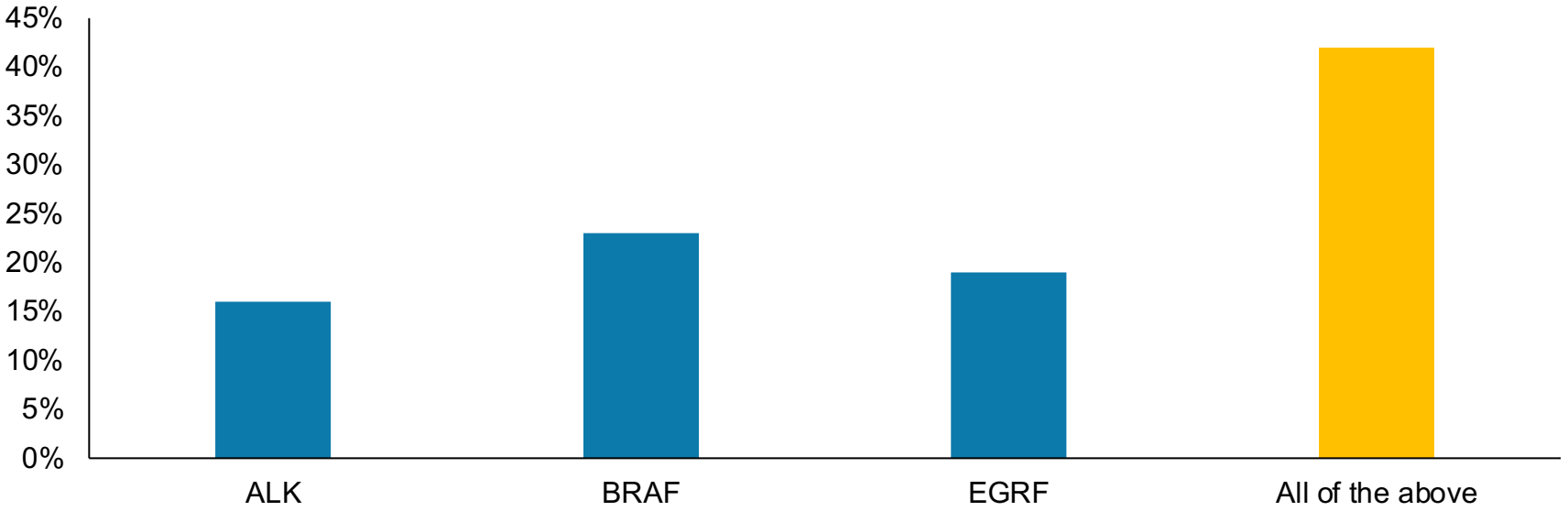
Mutation Testing for Metastatic NSCLC

Audience Response

Which of the following genomic alterations are recommended for molecular testing in NSCLC?

A. ALK
B. BRAF
C. EGFR
D. All of the above

Which of the following genomic alterations are recommended for molecular testing in NSCLC?



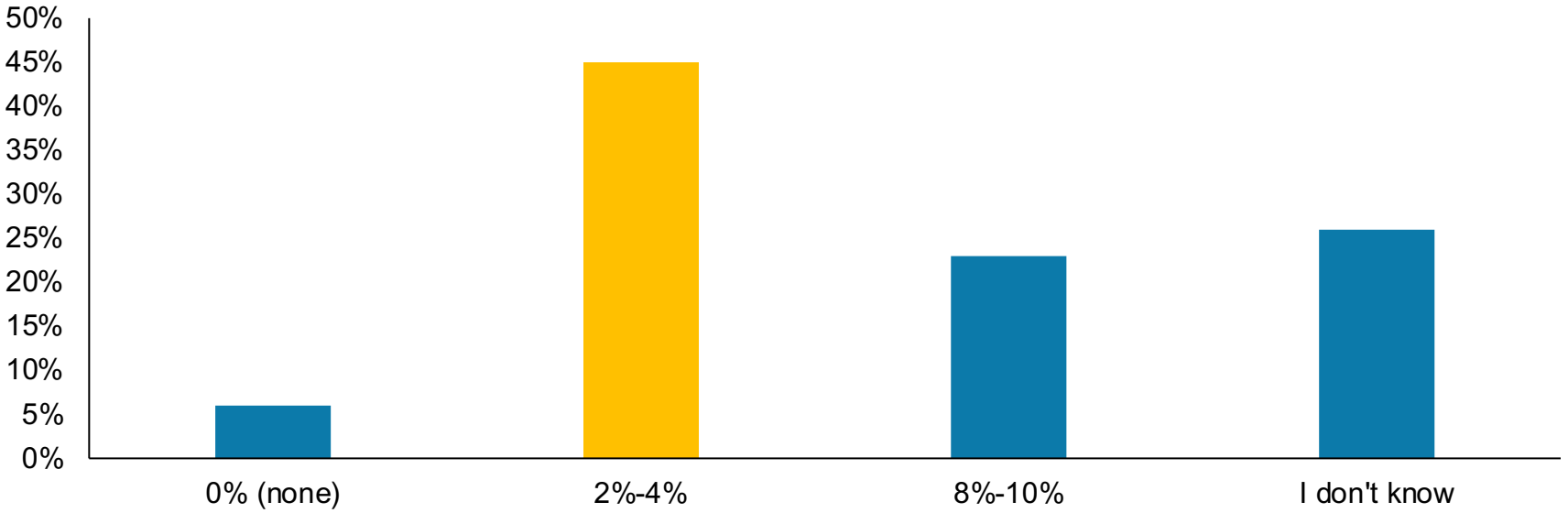
Results recorded on December 1, 2020

Audience Response

What is the observed rate of HER2 mutations in lung adenocarcinoma?

A. 0% (none)
B. 2%-4%
C. 8%-10%
D. I don’t know

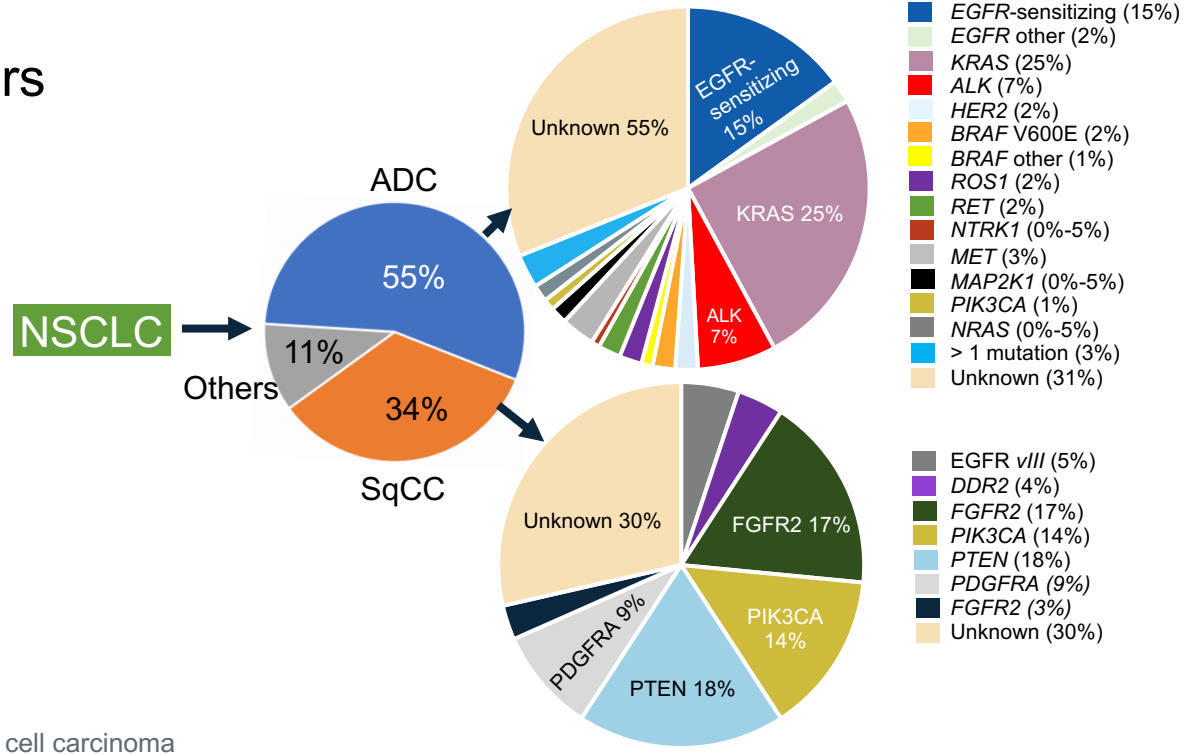
What is the observed rate of HER2 mutations in lung adenocarcinoma?



Results recorded on December 1, 2020

NSCLC: Complex Picture

- 85% of lung cancers
- Highly heterogeneous
- Majority presented in the advanced stage

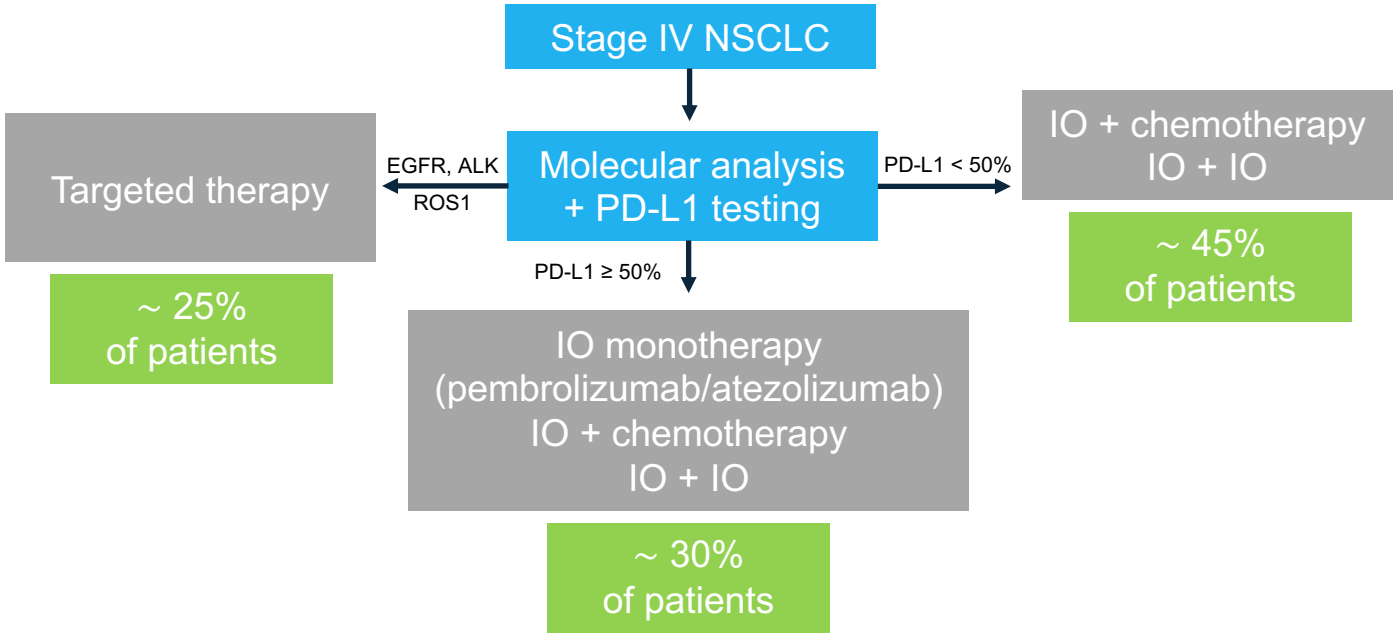


ADC = adenocarcinoma; SqCC = squamous cell carcinoma

Li T, et al. *J Clin Oncol*. 2013;31(8):1039-1049.; Bubendorf L, et al. *Eur Respir* Rev. 2017;26(144):170007.; Zappa C, Mousa SA. *Transl Lung Cancer Res*. 2016;5(3):288-300. Brainard J, Farver C. *Mod Pathol.* 2019;32(1):16-26.

Advanced NSCLC: Biomarkers and Actionable Mutations

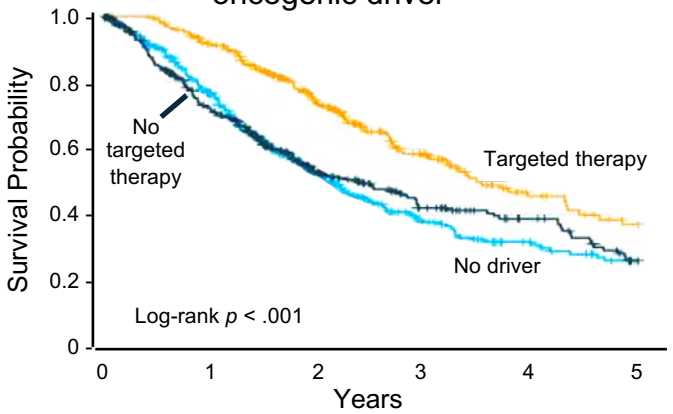
- EGFR
- ALK
- ROS
- BRAF V600
- MET exon 14
- NTRK
- RET
- HER2 (ERBB2)



Gregory LR. *J Natl Compr Canc Netw*. 2017;15(5S):686-688.; Kim SY, Halmos B. *Lung Cancer Manag*. 2020;9(3):LMT36.

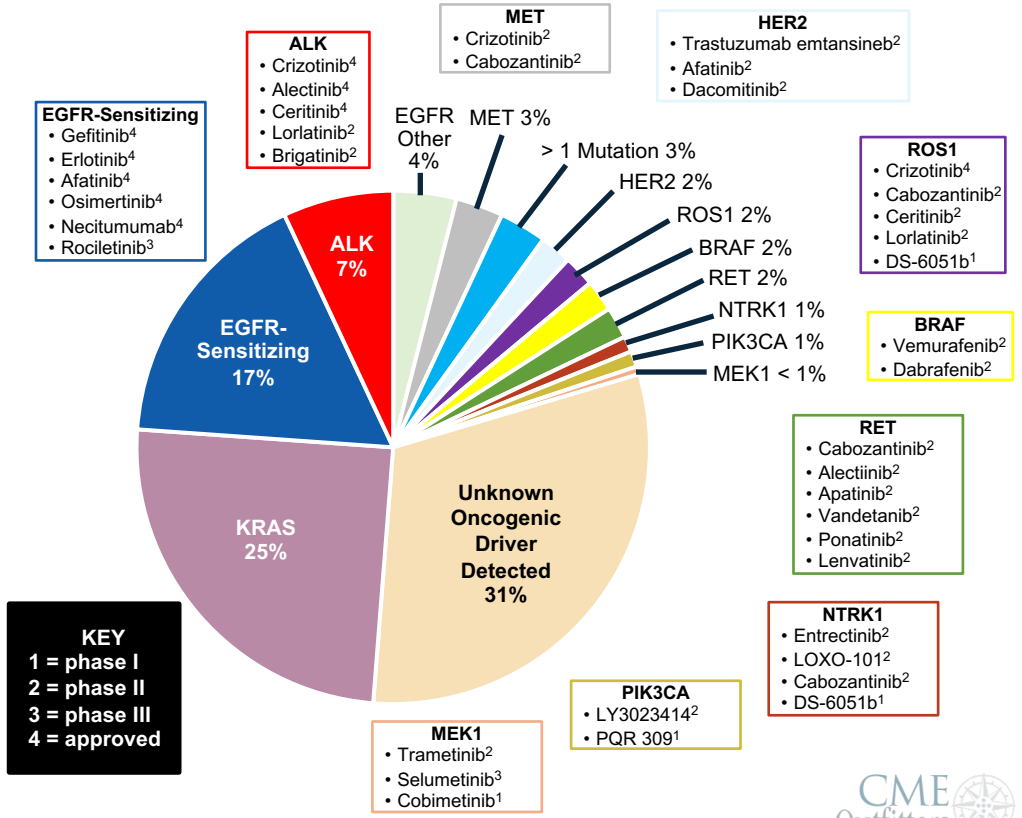
Targeting Actionable Mutations in NSCLC

Patients with an oncogenic driver mutation who did and did not receive targeted therapy, and patients without an oncogenic driver



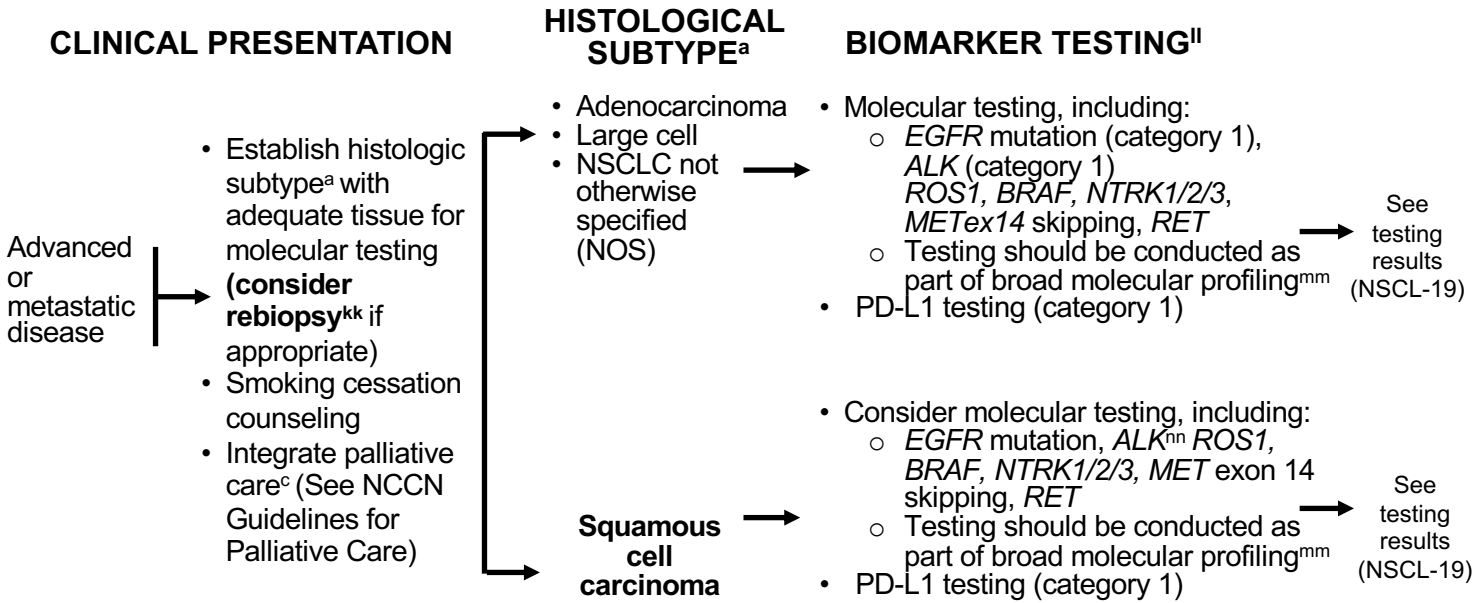
No. at risk

Patients with oncogenic driver						
No. targeted Therapy	318	205	110	64	43	20
Targeted. therapy	260	225	143	72	36	23
Patients with no driver	360	250	122	59	36	23



Kris MG, et al. *JAMA*. 2014;311(19):1998-2006.; Tsao AS, et al. *J Thoracic Oncol*. 2016;11(5):613-638.

Current NCCN Guideline Testing Recommendations Include Testing for Many Gene Mutations



Category/Level I (NCCN/ESMO Guidelines)
- EGFR
- ALK

Other Recommended/Level II
- ROS1
- BRAF
- NTRK 1/2/3
- METex14 skipping
- RET
- **Emerging Biomarkers and available therapies (NCCN)**
- *High level MET (Crizotinib, Capmatinib)*
- *HER2 (trastuzumab emtansine, trastuzumab deruxtecan)*

MET, RET, and NTRK have FDA-approved drugs now

[a]See Principles of Pathologic Review (NSCL-A). [c]Temel JS, et al. *N Engl J Med.* 2010;363:733-742. [kk]If there is insufficient tissue to allow testing for all of *EGFR, ALK, ROS1, BRAF, NTRK 1/2/3, MET,* and *RET*, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes. [ll]See Principles of Molecular and Biomarker Analysis (NSCL-H).

[mm]The NCCN NSCLC Guidelines Panel strongly advises broader molecular molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. See Emerging Biomarkers to Identify Patients for Therapies (NSCL-I). [nn]LAM VK, et al. *Clin Lung Cancer.* 2019;20:30-36.e3; Sands JM, et al. *Lung Cancer.* 2020;140:35-41.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ESMO = European Society for Medical Oncology; NCCN = National Comprehensive Cancer Network

Velcheti V, Pennell NA. *Ann Transl Med.* 2017;5(18):378.; National Comprehensive Cancer Network. NCCN. 2020. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.; Good Science Better Medicine Best Practice. ESMO. 2020. https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer.

Comparison of Molecular Assays for Biomarker Detection in NSCLC

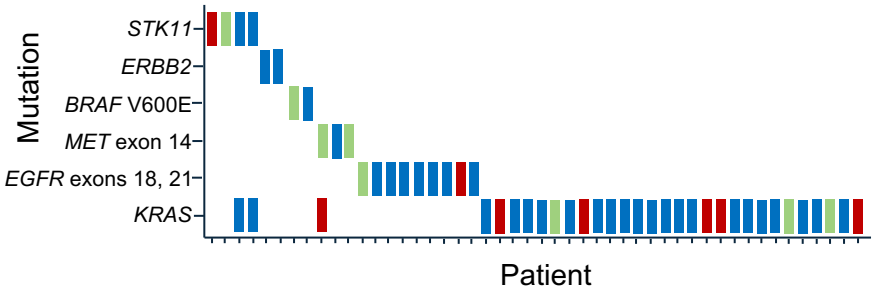
Molecular Methods	Variant Types				Sensitivity (%)	Turnaround Time
	Point Mutations	Small Deletion, Insertions	Copy Number Alterations	Rearrangements		
Sizing assays	+/−	✓				2-3 days
PCR and Sanger sequencing	✓	✓			20-50	3-4 days
PCR and pyrosequencing	✓	+/−			20-50	3-4 days
PCR and mass spectrometry	✓	+/−			1-10	3-4 days
PCR and single-base extension	✓				1-10	3-4 days
qPCR and digital PCR	✓	✓		✓	.00001	2-3 days
Allele-specific PCR	✓					1-2 days
FISH			+/−	✓	< 1	2-3 days
NGS: targeted amplicon capture	✓	✓			1-10	7-10 days
NGS: targeted hybridization capture	✓	✓	✓	+/− 1	1-5	15-20 days
NGS: whole exome	✓	✓	✓	+/− 1	Variable	Weeks
NGS: whole genome	✓	✓	✓	✓	Variable	Weeks

FISH = fluorescent in situ hybridization; NGS = next-generation sequencing; PCR = polymerase chain reaction; qPCR = quantitative PCR

Pennell NA, et al. *Am Soc Clin Oncol Educ Book*. 2019;(39):531-542.

Detecting Genomic Alterations in Advanced NSCLC-NGS

- ESMO recommends using tumor multigene NGS in patients presenting with advanced non-squamous NSCLC
- NCCN recommends NGS testing be performed via a broad, panel-based approach, most typically performed by NGS, when feasible
- High concordance with liquid biopsy (ctDNA) with tissue-based mutation analysis



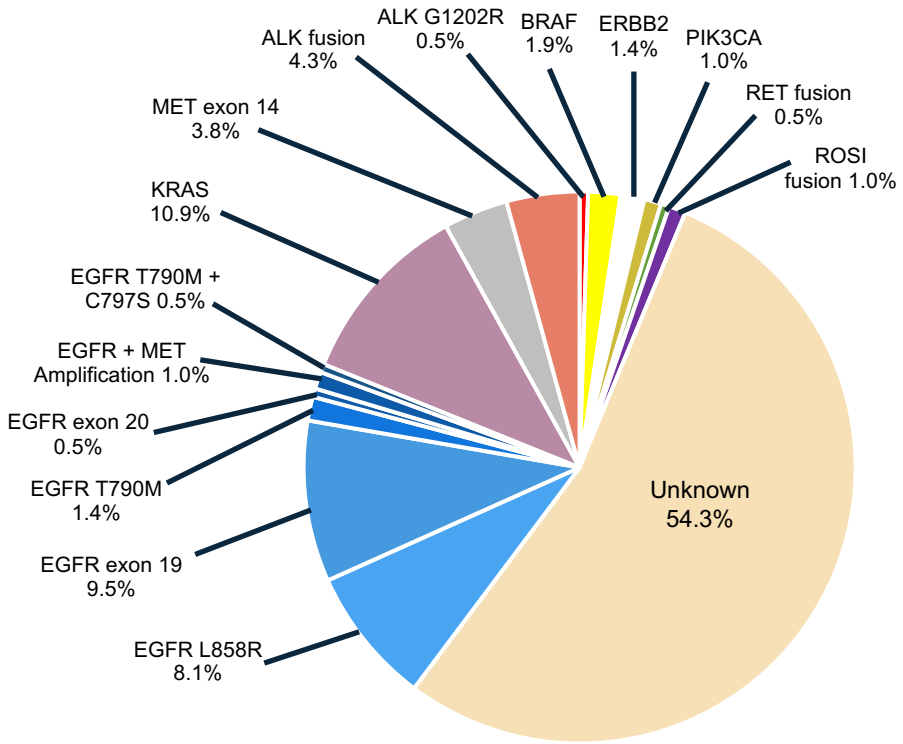
List of Genomic Alterations Level I/II/III According to ESCAT in Advanced Non-squamous

Gene	Alteration	Prevalence	ESCAT
EGFR	Common mutations (*Del*19, *L858R*) Acquired *T790M* exon 20 Uncommon *EGFR* mutations (*G719X* in exon 18, *L861Q* in exon 21, *S7681* in exon 20) Exon 20 insertions	15% (50%-60% Asian) 60% of *EGFR* mutant NSCLC 10% 2%	IA IA IB IIB
ALK	Fusions (mutations as mechanism of resistance)	5%	IA
MET	Mutations exon 14 skipping Focal amplifications (acquired resistance on EGFR TKI in *EGFR*-mutant tumors)	3% 3%	IB IIB
BRAF V600E	Mutations	2%	IB
ROS1	Fusions (mutations as mechanism of resistance)	1%-2%	IB
NTRK	Fusions	0.23%-3%	IC
RET	Fusions	1%-2%	IC
KRAS^{G12C}	Mutations	12%	IIB
ERBB2	Hotspot mutations Amplifications	2%-5%	IIB
BRCA 1/2	Mutations	1.2%	IIIA
PIK3CA	Hotspot mutations	1.2%-7%	IIIA
NRG1	Fusions	1.7%	IIIB

ESCAT = ESMO scale for Clinical Actionability of molecular targets

Mosele F, et al. *Ann Oncol*. 2020;31(11):1491-1505.; Remon J, et al. *JCO Precis Oncol*. 2019;3:PO.18.00211. ; NCCN. NSCLC v1.2021. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

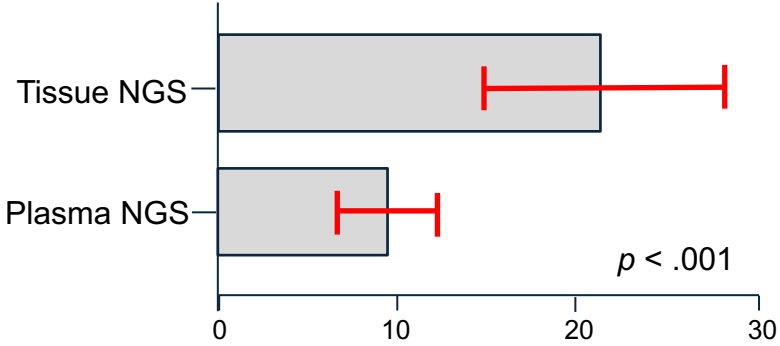
NSCLC Genetic Driver Mutation Identification by NGS



Genetic driver alteration identified by plasma next-generation sequencing (n = 210)

Tissue NGS	Plasma NGS
Slower turnaround time	Faster turnaround time
High concordance (89.6%)	Negative result is not confirmatory (60.6% concordance)

2 cases (-) in tissue NGS was (+) in plasma NGS

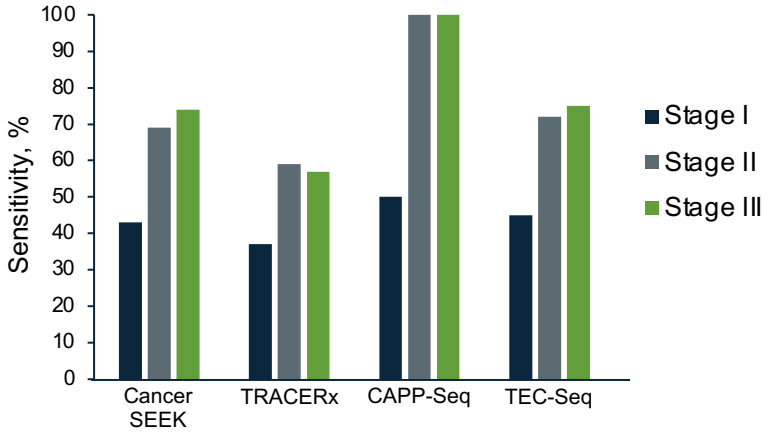


Turnaround time of plasma and tissue NGS; Plasma samples, n = 210; tissue samples, n = 107; The paired turnaround times were compared by a two-sided Wilcoxon signed-rank test

Sabari JK, et al. *J Natl Cancer Inst*. 2019;111(6):575-583.

Evolving Role of NGS in NSCLC

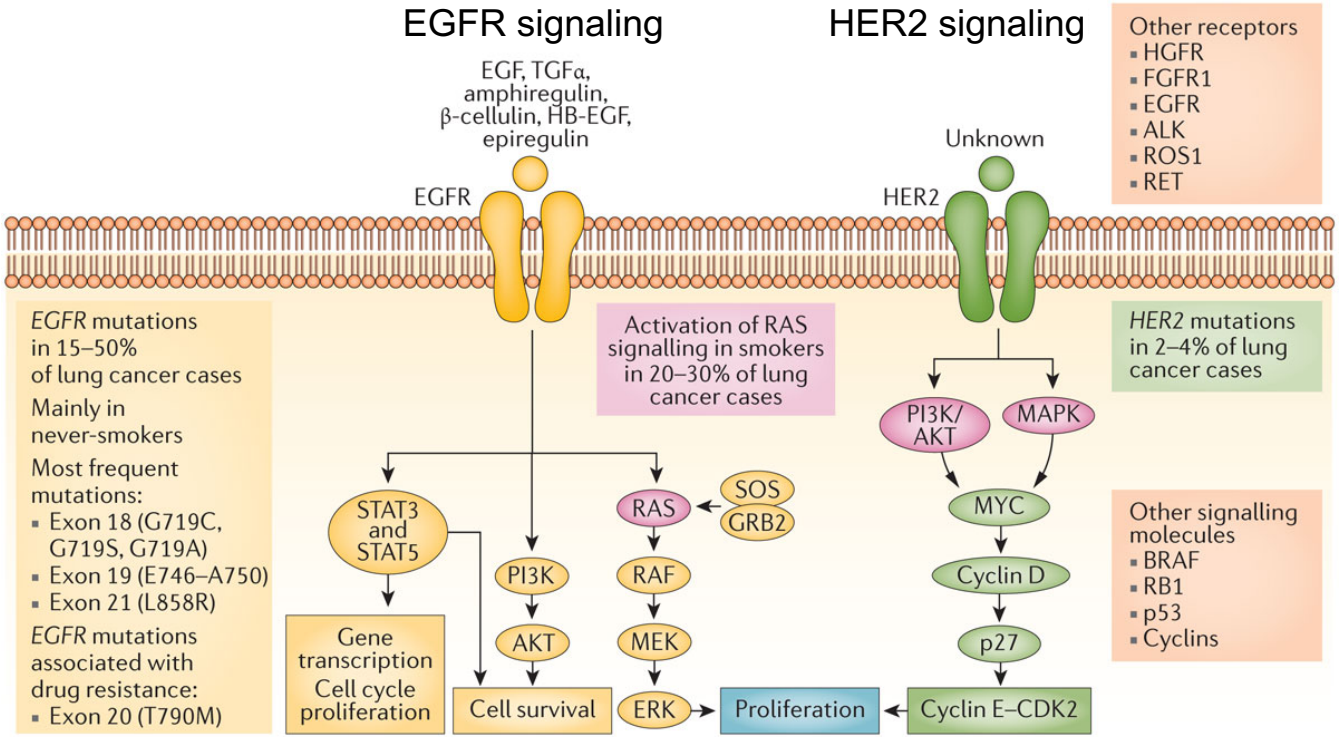
- Potential to help manage NSCLC in all stages of cancer
- ctDNA sensitivity is low in early stages but high in advanced stages
- cfDNA capable of identifying all guideline genomic biomarkers



			cfDNA		Tissue
Guideline-Recommended Genomic Biomarkers (Selected)	TCGA	% of Total Cohort	Frequency of Alteration (%)	% of Total Cohort	Frequency of Alteration (%)
EGFR mutation	11.30%	15.20%	16.00%	14.20%	17.30%
ALK fusion	1.30%	2.10%	2.20%	3.20%	4.00%
ROS1 fusion	1.70%	0.00%	0.00%	0.70%	1.20%
BRAF mutation (V600E)	7.00%	0.70%	0.70%	0.70%	2.10%
RET fusion	0.90%	1.10%	1.10%	0.00%	0.00%
ERBB2 mutation	1.70%	1.10%	1.10%	0.40%	1.60%
MET exon 14 skipping variant	4.30%	3.50%	3.70%	1.80%	7.50%
MET amplification	2.20%	5.30%	5.60%	0.40%	1.60%
KRAS mutation	32.20%	31.60%	33.20%	8.50%	32.90%

Guibert N, et al. *Eur Respir Rev*. 2020;29(155):190052.; Leighl NB, et al. *Clin Cancer Res*. 2019;25(15):4691-4700.

Receptor Signaling in NSCLC: Druggable Targets



Mar N, et al. *Lung Cancer*. 2015;87(3):220-225.; Jebbink M, et al. *Cancer Treat Rev*. 2020;86:101996.

HER2 in Lung Adenocarcinoma

- Protein overexpression (IHC 2+ or 3+) in 12%-20% of cases
- Amplification in ~ 3% of cases, around 10% of cases in EGFR TKI resistance
  - HER2 amplification and mutations usually do not occur together
- Activating mutations in ~ 2%-4% of cases
- How to define HER2-positive lung cancer?
- Which of them are suitable for treatment with anti-HER2 agents?

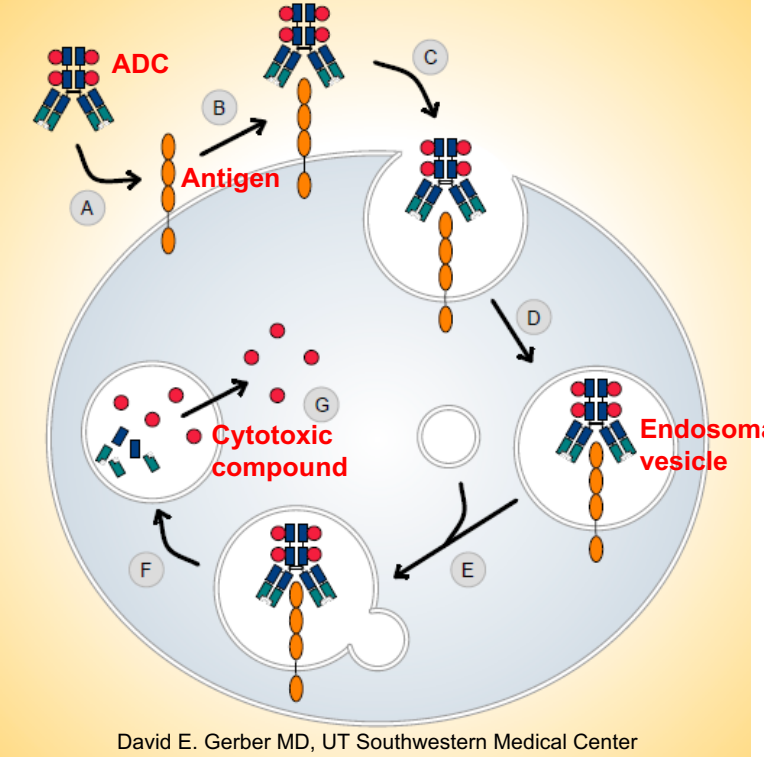
Li BT, et al. *J Thorac Oncol.* 2016;11(3):414-419.; Nakamura H, et al. *Int J Cancer.* 2003;103(1):61-66.; Yoshizawa A, et al. *Lung Cancer.* 2014;85(3):P373-P378.; Ekman S. *Ann Oncol.* 2019;30(3):P353-P355.

ADCs in NSCLC

Mechanism and Characteristics of ADCs in NSCLC

An Animated Tour

ADCs Deliver Lethal Payloads to the Target



A. Antigen access via circulation

B. Antigen binding

C. Antigen-ADC complex internalization

D. Incorporation into endosomal vesicles

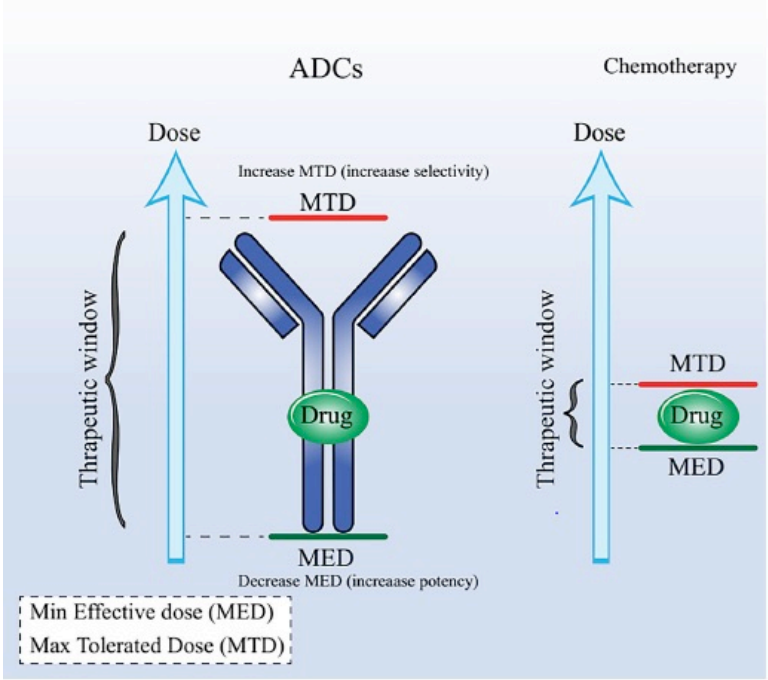
E. Processing along endosomal-lysosomal pathway

F. Degradation in acidic and proteolytic rich environment

G. Intracellular release of cytotoxic compound

Parslow AC, et al. *Biomedicines*. 2016;4(3):14.

ADCs Can Extend the Therapeutic Window



Compared to conventional chemotherapy, ADCs can ↑ efficacy and ↓ toxicity:

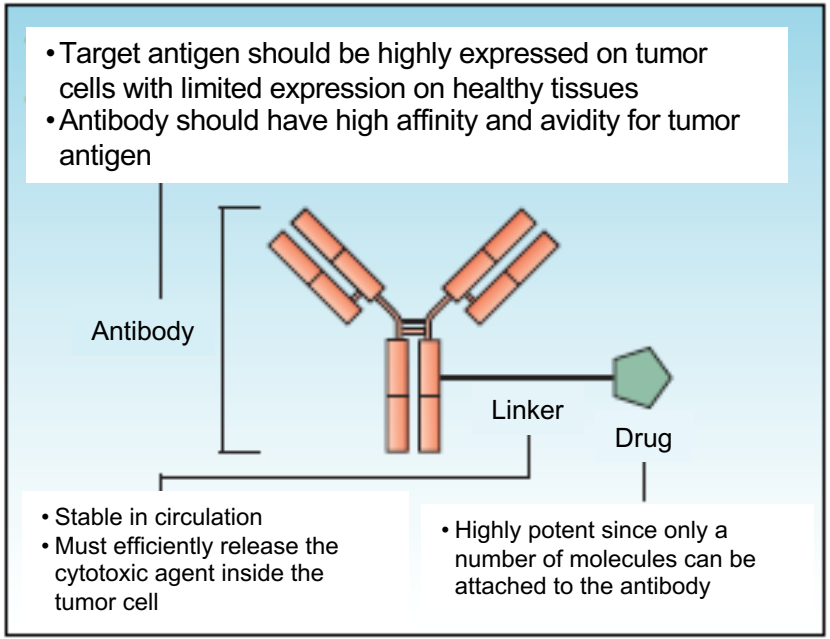
- Targeted delivery of drugs to cancer cells → ↑ drug doses in tumor microenvironment → ↓ **minimum effective dose (MED)**
- Fewer drug molecules within normal, non-target tissues → ↑ **maximum tolerated dose (MTD)**

Nasiri H, et al. *J Cell Physiol*. 2018;233:6441-6457.

Tumor and ADC Characteristics Impact Efficacy and Toxicity

Tumor Characteristics

- Target antigen highly expressed on tumor
- Limited expression of target antigen on healthy tissues
- Target antigen not shed at high levels
- Target antigen-ADC complex internalized upon binding



ADC Characteristics

- Antibody has high affinity, avidity for target antigen
- Linker stable in circulation but efficiently releases payload inside tumor cell
- Highly potent drug

Thomas A, et al. *Lancet Oncol*. 2016;17(6):e254-e262.

Case Study: Meet Joanna

- Joanna is a 66-year-old woman with relapsed small cell lung cancer (SCLC) after platinum-etoposide and topotecan
- Treated with anti-DLL3 antibody-drug conjugate 4/2017-6/2017
- Excellent response to therapy but subsequent development of target-related toxicities of pleural, pericardial effusions

Select ADCs in NSCLC and Other Solid Tumors

Target	ADC	Tumors	Clinical Trial Number	Phase
Axl	BA3011 (CAB-AXL)	NSCLC, other solid tumors	NCT03425279	I, II
Axl	Enapotamab vedotin	NSCLC, other solid tumors	NCT02988817	I, II
B7-H3	MGC018	NSCLC, other solid tumors	NCT03729596	I, II
CD166	CX-2009	NSCLC, other solid tumors	NCT03149549	I, II
CD205/Ly75	MEN1309	Metastatic NSCLC, other solid tumors	NCT03403725	I
CD71	CX-2029	NSCLC, other solid tumors	NCT03543813	I, II
cMet	ABBV-399 (telisotuzumab vedotin)	NSCLC	NCT02099058, NCT03539536	I
cMet	SHR-A1403	NSCLC, other solid tumors	NCT03856541	I
cMet	TR1801	NSCLC, other solid tumors	NCT03859752	I
EGFR	AVID100	NSCLC, other solid tumors	NCT03094169	I, II
HER2	A166	Lung cancer, other HER2+ cancers	NCT03602079	I, II
HER2	DS-8201a	NSCLC, HER2 positive	NCT03505710, NCT02564900	II
HER2	FS-1502 (trastuzumab monomethyl auristatin F)	NSCLC, breast and other solid tumors	NCT03944499	I
HER2	SYD985 (trastuzumab vc-seco-DUBA)	NSCLC, other solid tumors	NCT02277717	I
HER2	XMT-1522	NSCLC, breast cancer	NCT02952729	I
HER3	U3 1402	NSCLC	NCT03260491	I
IGF-1R	W0101	NSCLC, other solid tumors	NCT03316638	I, II
mesothelin	BAY 94-9343 (anetumab ravtansine)	NSCLC, mesothelin positive, others	NCT01439152, NCT03455556	I
mesothelin	BMS-986148	NSCLC, other solid tumors	NCT02341625	I, II
ROR2	BA3021 (CAB-ROR2)	NSCLC, other solid tumors	NCT03504488	I, II
SLC34A2/NaPi2b	XMT1536	NSCLC, ovarian cancer	NCT03319628	I
Trop-2	IMMU-132 (sacituzumab govitecan)	SCLC, NSCLC, other epithelial cancers	NCT01631552	I, II

Deneka AY, et al. *Cancers*. 2019,11(9):1297.

ADCs Targeting Select Genomic Alterations in NSCLC

ADC	Target	Phase (CT)
Trastuzumab emtansine (T-DM1)	HER2	II (NCT02289833)
Trastuzumab emtansine (T-DM1)	HER2	II, in progress (NCT02675829)
Trastuzumab deruxtecan (DS-8201a)	HER2	I, in progress (NCT02564900)
Trastuzumab deruxtecan (DS-8201a)	HER2	II, in progress (NCT03505710)
U3-1402	HER3	I, in progress (NCT03260491)
Telisotuzumab vedotin (ABBV-399)	c-Met	I/Ib in progress (NCT02099058)
DS-1062	TROP2	I, in progress (NCT03401385)
Sacituzumab govitecan	TROP2	I (NCT01631552)

Payan S, et al. *Target Oncol*. 2020;15(4):429-448.

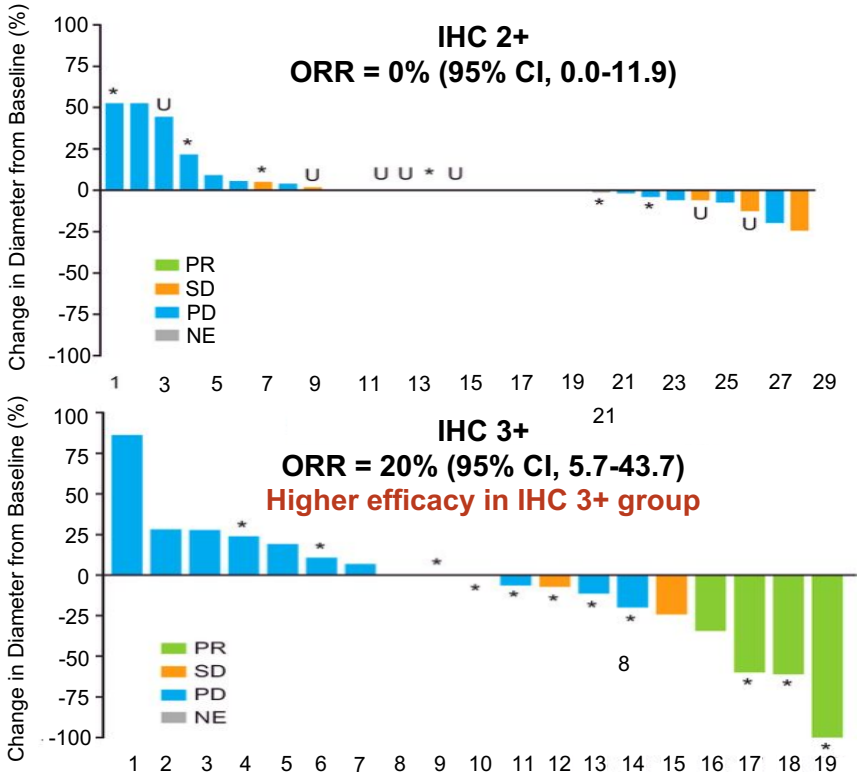
Trastuzumab Emtansine (T-DM1) in Previously Treated HER2 Metastatic NSCLC (NCT02289833)

- Phase II
- Previously treated advanced HER-2 overexpressing (IHC 2+ or 3+)
- Age ≥ 18
- All patients received T-DM1 (3.6 mg/kg intravenously every 3 weeks)
- Median treatment duration was 3.6 months (0-24.8 months)

	T-DM1 (N = 49)
Any AE	45 (92%)
Serious AE	10 (20%)
Withdrawal due to AE	2 (4%)
Death as a result of AE	0
Death as a result of AE related to study drug	0

Peters S, et al. *Clin Cancer Res*. 2019;25(1):64-72.

Efficacy of T-DM1 in Previously Treated HER2 Metastatic NSCLC



Parameter	T-DM1	
	Patients with IHC 2+ (N = 29)	Patients with IHC 3+ (N = 20)
CR	0	0
PR	0	4 (20%)
SD	8 (28%)	4 (20%)
PD	16 (55%)	11 (55%)
DCR	8 (28%)	8 (40%)
ORR	0	4 (20%)
PFS	2.6 months	2.7 months

CR = complete remission; DCR = disease control rate; ORR = objective response rate; PD = progressive disease; PFS = progression free survival; PR = partial remission; SD = stable disease

Peters S, et al. *Clin Cancer Res*. 2019;25(1):64-72.

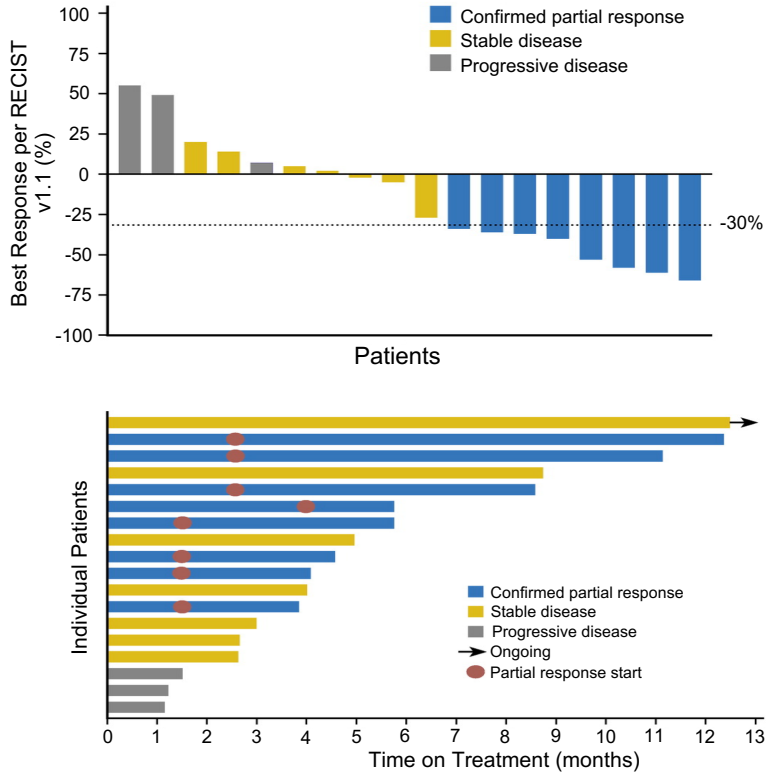
T-DM1 in HER2-Mutant Lung Cancers (NCT02675829):Ongoing Trial

- Phase II basket trial
- Patients with metastatic lung adenocarcinoma
- Median age 64 (47-74)
- All patients received T-DM1 (3.6 mg/kg intravenously every 3 weeks
- Median treatment duration was 4 months

	T-DM1 (N = 18)
Any AE	YES Elevated AST, ALT (39%) Thrombocytopenia (33%)
Serious AE	YES Grade 3-4 anemia (6%)
Withdrawal due to AE	0
Death as a result of AE	0
Death as a result of AE related to study drug	0

AE = adverse effect(s); ALT = alanine aminotransferase; AST = aspartate aminotransferase
Li BT, et al. *J Clin Oncol*. 2018;36(24):2532-2537.

Efficacy of T-DM1 in HER2-Mutant Lung Cancers

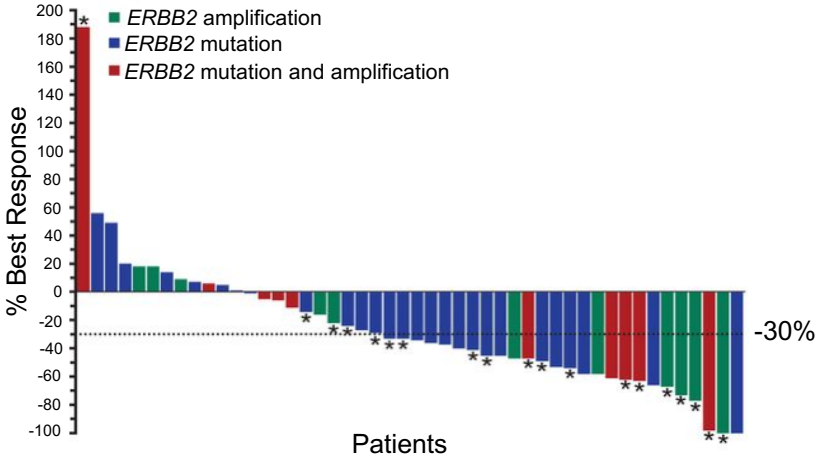


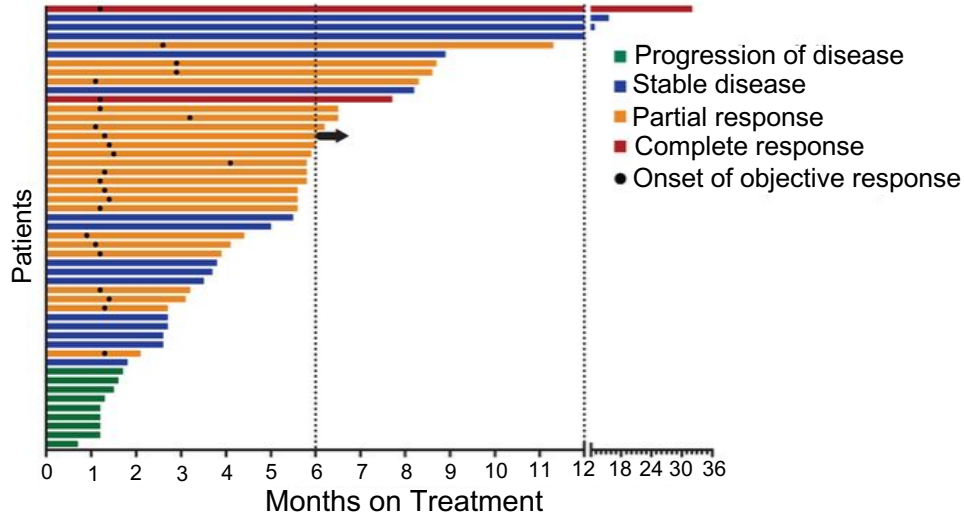
Parameter	T-DM1 (N = 18)
CR	0
PR	8 (44%)
SD	7 (39%)
PD	3 (17%)
DCR	15 (83%)
ORR	8 (44%)
PFS	5 months

Li BT, et al. *J Clin Oncol*. 2018;36(24):2532-2537.

Study Update: T-DM1 in HER2-Mutant and/or Amplified Lung Cancers (NCT02675829)

- N = 49 (including 18 from previous report)





Parameter	N = 49
ORR	25 (51%)
PFS	5 months

Similar ORR for both HER2 mutations and HER2 amplifications

Li BT, et al. *Cancer Discov*. 2020;10(5):674-687.

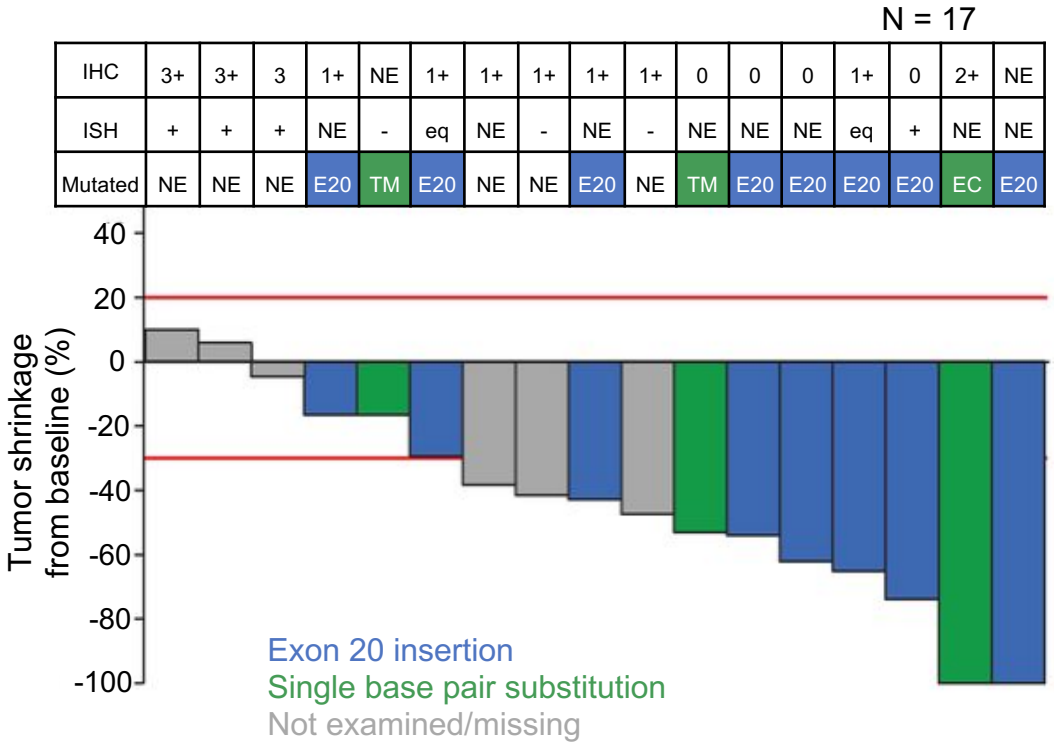
Trastuzumab deruxtecan(T-DXd) Targeting HER2 in Multiple Advanced Solid Tumors (NCT02564900): Ongoing Trial

- Phase I dose expansion in pre-treated HER-2–expressing (IHC≥ 1+) patients
- Median age 59
- Median treatment duration 10.6 months
- *HER2* mutation 61.2% (11/18)
- Most common *HER2* mutations among patients with NSCLC were exon 20 insertions 44.4% (8/18)
- Among the 18 patients with NSCLC, 27.8% (5/18) had received a prior HER2-targeted regimen, 22.2% (4/18) had received a prior EGFR inhibitor, and 5.6% (1/18) had received a prior anaplastic lymphoma kinase inhibitor

	T-DXd (DS-8201) (N = 18) NSCLC
Any AE	18 (100%)
Serious AE related to study drug	2 (11.2%)
Withdrawal due to AE	NR
Death as a result of AE	1 (5.6%)
Death as a result of AE related to study drug	1 (5.6%)

Tsurutani J, et al. *Cancer Discov*. 2020;10(5):688-701.

Efficacy of T-DXd Targeting HER2 in Multiple Advanced Solid Tumors



Parameter	T-DXd (DS-8201)	
	All Patients (N = 18)	Patients with HER-2 Mutant NSCLC (N = 11)
CR	0	0
PR	10 (55.6%)	8 (72.7%)
SD	4 (22.2%)	2 (18.2%)
PD	3 (16.7%)	1 (9.1%)
DCR	14 (77.8%)	10 (90.9%)
ORR	10 (55.6%)	8 (72.7%)
PFS	11.3 months	

Tsurutani J, et al. *Cancer Discov*. 2020;10(5):688-701.

T-DXd in HER2-Mutatated Metastatic NSCLC (DESTINY-Lung01) (NCT03505710): Ongoing Trial

- Phase II in patients with non-squamous NSCLC with HER2-overexpressing or HER2-activating mutants
- Median age 63 (34-83)
- 6.4 mg/kg every 3 weeks
- Median treatment duration 7.75 months
- Data presented for HER-2 mutated group
- Most common *HER2* mutations in the kinase domain (90.5%)
- Most patients (90.5%) had prior platinum-based therapy and 54.8% had anti PD-1 or PD-L1 treatment

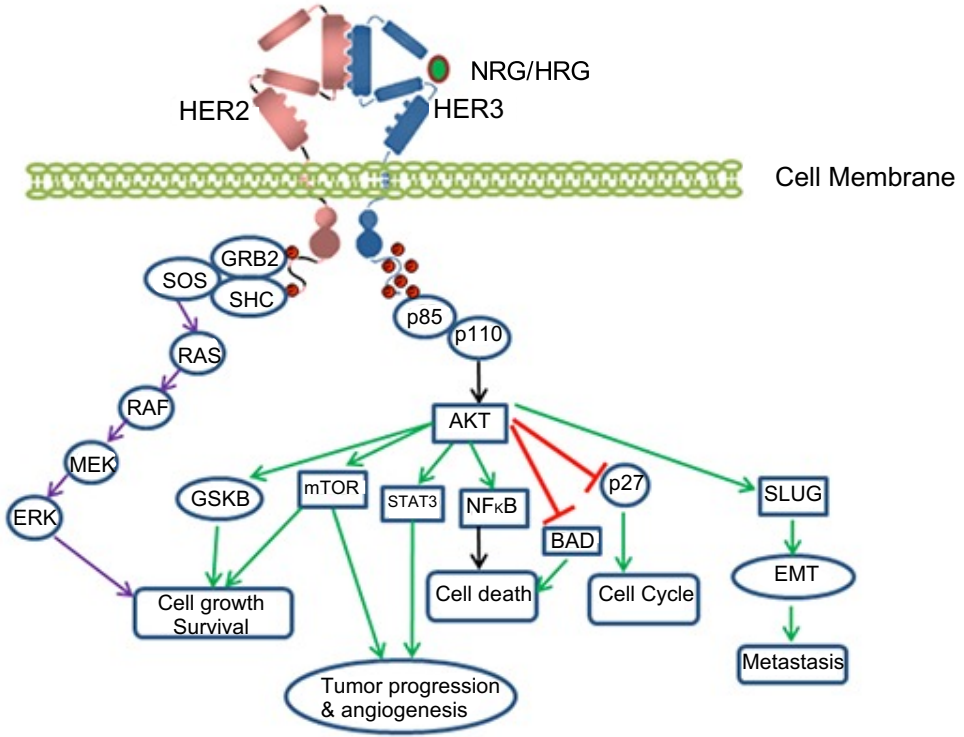
	T-DXd (DS-8201) (N = 42)
Any AE	42 (100%)
Serious AE related to study drug	22 (52.4%)
Withdrawal due to AE	10 (23.8%)
Death as a result of AE	0
Death as a result of AE related to study drug	0

Parameter	N = 42
ORR	61.9%
PFS	14 months

Smit EF, et al. *J Clin Oncol*. 2020;38(suppl).Abstract No. 9504.

HER3 Targeting ADCs in NSCLC

- HER3 (ERBB3) is a member of the EGFR family
- Dimerizes with HER2 to activate oncogene signalling via PI3K/AKT, MAPK and JAK/STAT pathways
- HER3 activation leads to treatment failure
- Target for ADCs in multiple malignancies



Mishra R, et al. *Oncol Rev.* 2018;12(1):355.

Patritumab Deruxtecan (U3-1402) Targeting HER3 in EGFR-Mutated NSCLC (NCT03260491): Ongoing Trial

- Phase I dose escalation and dose expansion in advanced EGFRm NSCLC after failure of EGFR TKI and platinum-based chemotherapy
- Age ≥ 18 (United States) or ≥ 20 (Japan)
- Median treatment cycles 3 (1-19)
- 28 patients continuing at data cutoff

	Patritumab Deruxtecan (U3-1402) (N = 56)
Any AE	YES
Serious AE related to study drug	YES Thrombocytopenia 25% Neutropenia 16%
Withdrawal due to AE	0
Death as a result of AE	0
Death as a result of AE related to study drug	0

Yu HA, et al. *Ann Oncol*. 2020;31(Suppl 4):S1189-S1190.

Efficacy of U3-1402 Targeting HER3 in EGFR-Mutated NSCLC: Ongoing Trial

- 5.6 mg/kg
- 22/56 (39%) patients had best percentage decrease in sum of tumor diameters ≥ 30%
- Efficacy was observed in patients with several mechanisms of resistance including EGFR, C797S, MET amp, HER2m, BRAF fusion, and PIK3CAm

Parameter	Patritumab Deruxtecan (U3-1402) (N = 56)
CR	1 (2%)
PR	13 (23%)
SD	25 (45%)
PD	9 (16%)
DCR	39 (70%)
ORR	14 (25%)

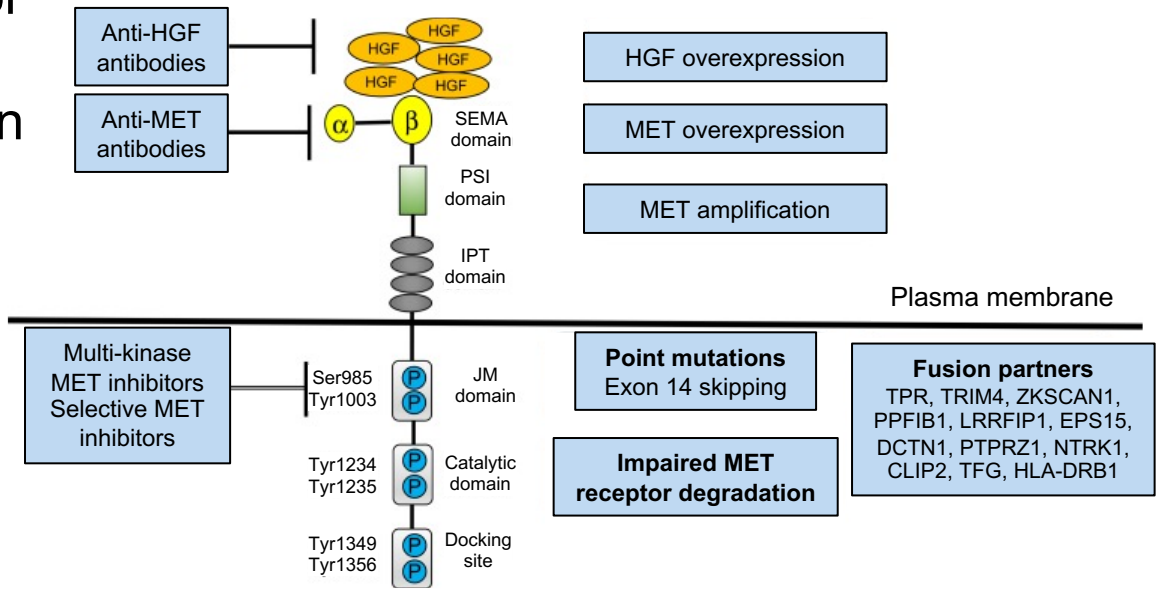
Yu HA, et al. *Ann Oncol*. 2020;31(Suppl 4):S1189-S1190.

CME Outfitters
CONTINUING MEDICAL EDUCATION

Faculty Discussion

c-MET Targeting ADCs in NSCLC

- c-MET is an HGF receptor
- Activation leads to excessive cell proliferation via multiple pathways including PI3K/AKT, RAS/ERK/MAPK and Wnt/β-catenin
- Overexpression/mutation of c-MET in NSCLC may lead to tumor invasion and metastasis



Liang H, Wang M. *Onco Targets Ther.* 2020;13:2491-2510.

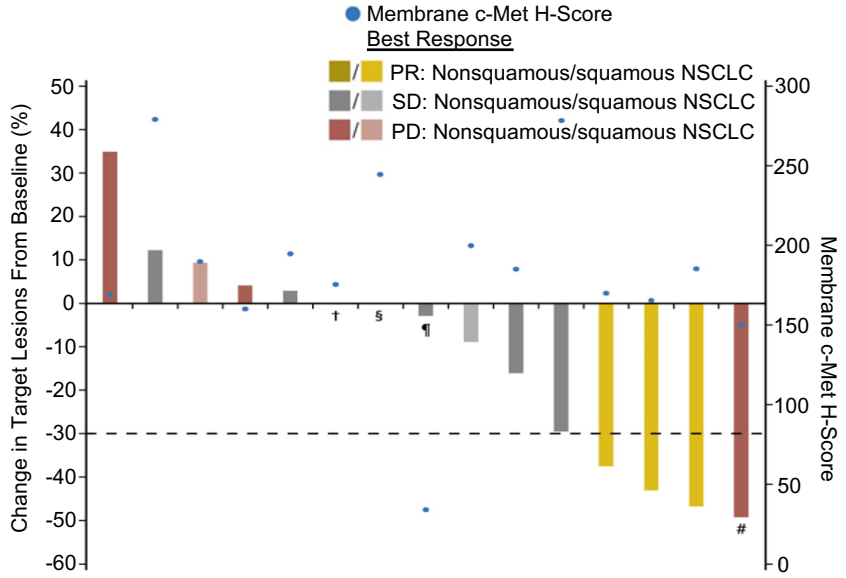
Telisotuzumab Vedotin (ABBV-399/Teliso-V) Targeting c-Met in Patients with Advanced Solid Tumors (NCT02099058): Ongoing Trial

- Phase I dose escalation study in advanced solid tumors including NSCLC
- NSCLC with c-MET + IHC H-score ≥ 150)
- 0.15 mg to 3.3 mg/kg
- IV dosing every 3 weeks

	ABBV-399/Teliso-V (N = 48) NSCLC (N = 16)
Any AE	46 (96%)
Serious AE related to study drug	2 (4%)
Withdrawal due to AE	11 (22.9%)
Death as a result of AE	4 (8%)
Death as a result of AE related to study drug	0 (0)

Strickler JH, et al. *J Clin Oncol*. 2018;36(33):3298-3306.

Efficacy of ABBV-399 Targeting c-Met in Patients with Advanced Solid Tumors



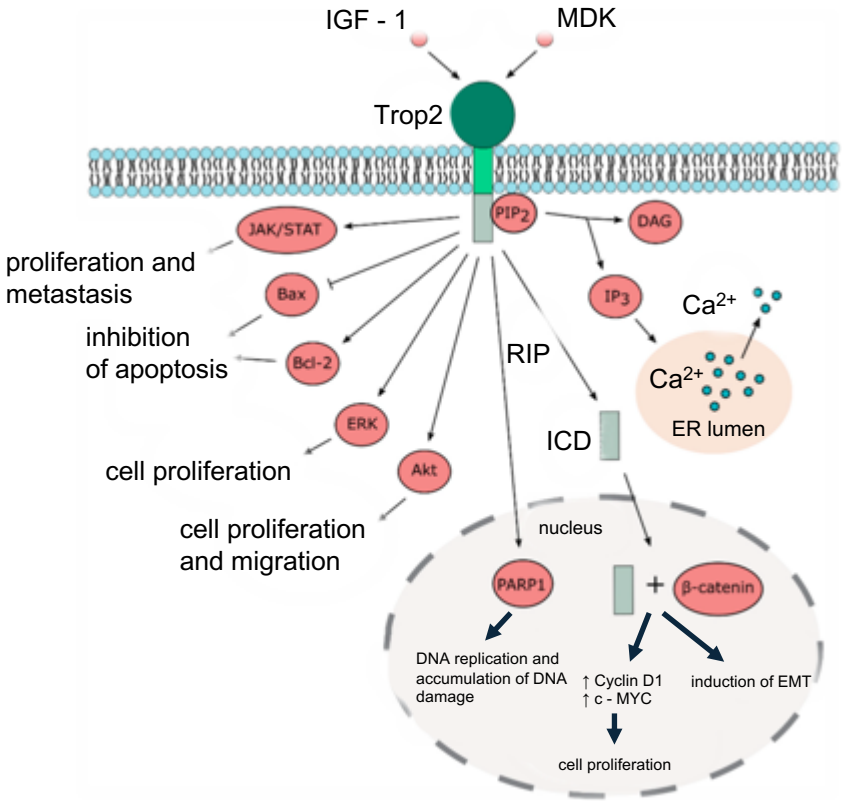
Patient No.	42	26	46	41	35	40	43	15	47	30	19	45	48	36	44
NSCLC histology	Non-SQ	Non-SQ	SQ	Non-SQ	Non-SQ	Non-SQ	Non-SQ	Non-SQ	SQ	Non-SQ	Non-SQ	SQ	SQ	SQ	Non-SQ
C-MET H-score	170	280	190	160	195	175	245	34	200	185	279	170	165	185	150
MET RNA level (FPKM)	33	171	15	18	28	NA	61	NA	37	NA	NA	15	7	28	27

Parameter	ABBV-399/Teliso-V Patients with cMet-Positive NSCLC (N = 16)
CR	0
PR	3 (18.8%)
SD	6 (37.5%)
PD	5 (31.3%)
DCR	9 (56.3%)
ORR	18.8 %
PFS	5.7 months

Strickler JH, et al. *J Clin Oncol*. 2018;36(33):3298-3306.

Trophoblast Cell-Surface Antigen 2 (TROP2) Targeting ADCs in NSCLC

- TROP2 is a glycoprotein which mediates cell proliferation, growth and calcium mobilization via a complex network of signalling pathways
- Overexpression correlates with poor prognosis in some malignancies including NSCLC



Lenárt S, et al. *Cancers (Basel)*. 2020;12(11):E3328.

DS-1062 in Targeting TROP2 in Advanced NSCLC (NCT03401385): Ongoing Trial

- Phase I dose escalation and dose expansion with unresectable NSCLC refractory to/relapsed from standard treatment with measurable disease (RECIST v1.1) and available tumor for retrospective TROP2 evaluation were eligible
- Age ≥ 18 (United States) or ≥ 20 (Japan)
- Median treatment cycles 3 (1-19)
- Treatment was well tolerated up to 8 mg/kg, and a dose effect on antitumor activity was observed over 2.0-10.0 mg/kg in heavily pretreated patients with prior progression on standard treatment

	(DS-1062) (N = 95)
Any AE	91 (96%)
Serious AE related to study drug	17 (18%)
Withdrawal due to AE	NR
Death as a result of AE	0
Death as a result of AE related to study drug	0

Parameter	N = 88 (response-evaluable)
PR	22 (25%)

Lisberg AE, et al. *J Clin Oncol*. 2020;38(suppl). Abstract No. 9619.

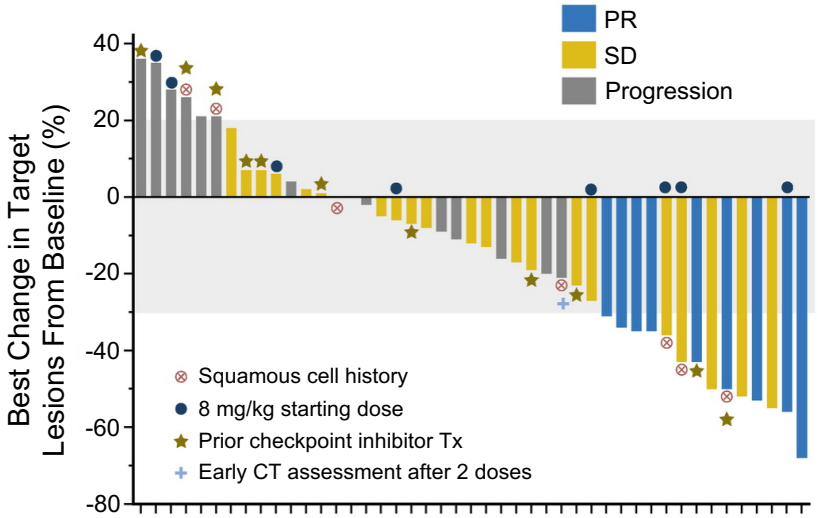
Sacituzumab Govitecan (IMMU-132) Targeting Trophoblast Cell-Surface Antigen 2 (TROP2) in Advanced NSCLC (NCT01631552)

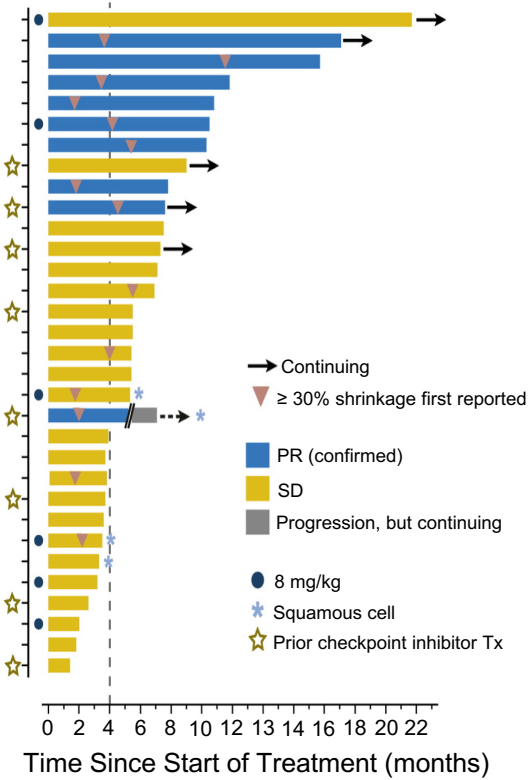
- Pretreated patients with metastatic NSCLC
- Median age 64 (40-68)
- Not preselected on the basis of TROP-2 expression on their tumors
- TROP-2 is not a predictive biomarker for response

	Sacituzumab Govitecan (IMMU-132) (N = 54)
Any AE	YES
Serious AE related to study drug	YES Neutropenia 28% Leukopenia 9% Pneumonia 9% Diarrhea 7%
Withdrawal due to AE	2 (3.7%)
Death as a result of AE	0
Death as a result of AE related to study drug	0

Heist RS, et al. *J Clin Oncol*. 2017;35(24):2790-2797.

Efficacy of IMMU-132 Targeting TROP2 in Advanced NSCLC





Parameter	Sacituzumab Govitecan (IMMU-132) Evaluable Patients (N = 47)
CR	0
PR	9 (19%)
SD	23 (49)
PD	15 (32%)
DCR (PR + SD ≥ 4 months)	20 (43%)
ORR	9 (19%)
PFS	5.2 months

Heist RS, et al. *J Clin Oncol*. 2017;35(24):2790-2797.

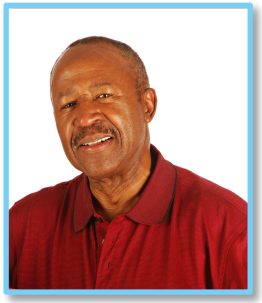
CME Outfitters
CONTINUING MEDICAL EDUCATION

Faculty Discussion

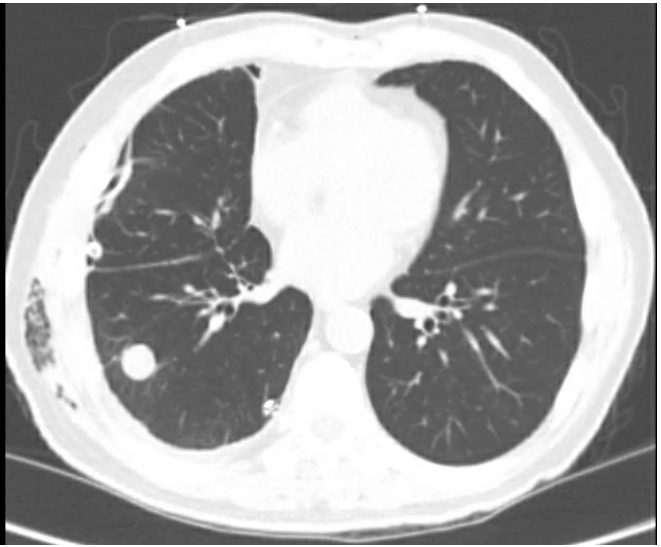
Takeaways for ADCs in NSCLC

Cancer Care During COVID-19

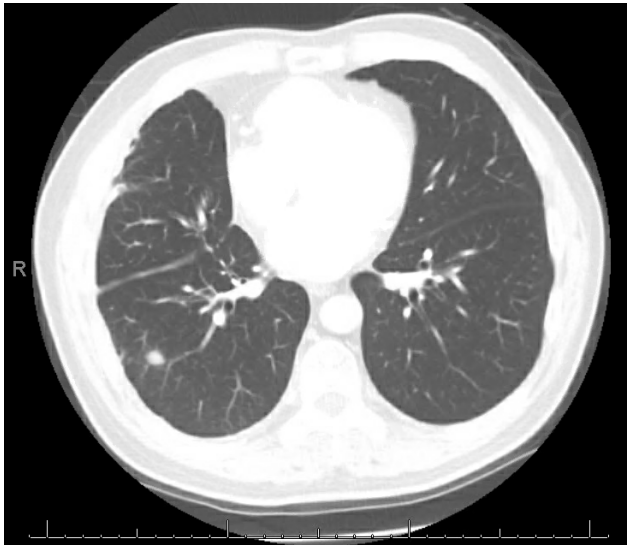
Case Study: Meet Frank



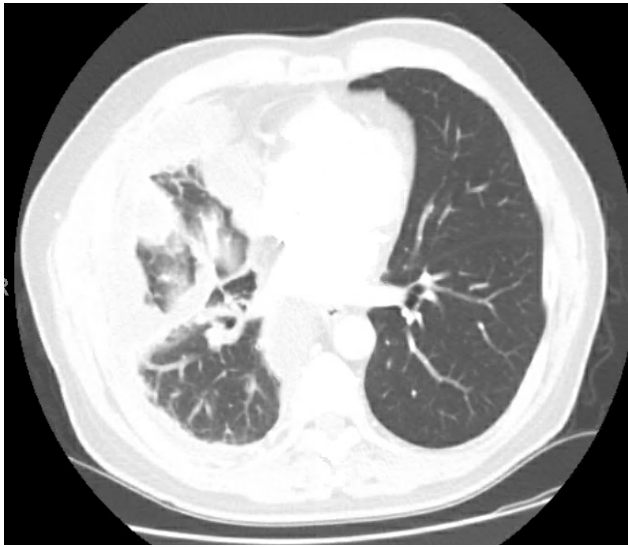
- 63-year-old man with mesothelioma
- Received cisplatin-pemetrexed pre-op chemotherapy 12/2019-2/2020 with excellent response
- Offered surgery 3/2020 but chose to delay due to COVID concern
- Returned to clinic 8/2020, with imaging showing profound growth in tumor, now unresectable
- Chemotherapy restarted with hope to render resectable again



December 2019



March 2020



August 2020

Impact of COVID-19 on Clinical Trials

FDA Guidance (updated September 21, 2020)

- Purpose: Protect trial participants and manage study conduct
- Recognized challenges: Quarantines, site closures, travel limitations, interruptions to supply chain of investigational product, or possibility of staff/patients becoming infected with COVID-19
- Thus, difficulties meeting protocol-specified procedures (administering treatment; adhering to protocol-mandated visits, lab tests, imaging studies
- Consider: Telephone or video visits; local (i.e., near patient's home) lab and imaging studies; delaying some assessments; alternative sites for treatment administration; remote monitoring
- *Remains in effect only during the COVID-19–related public health emergency*

U.S. Food and Drug Administration (FDA) Website. 2020. https://www.fda.gov/media/136238/download.

Impact of COVID-19 on Clinical Trials

NIH Central IRB (CIRB) Guidance

- Clinical evaluations, blood tests, radiology studies, administration of non-investigational study treatments may be administered by non-study local healthcare providers
- Can obtain informed consent remotely
- Can use electronic signatures

NCI Cancer Therapy Evaluation Program (CTEP) Guidance

- “Virtual” or “telemedicine” visits may be used
- Protocol-required laboratory/imaging tests and treatment may be delayed
- Local healthcare providers may perform study follow-up
- May ship oral study therapy directly to patients’ homes

National Cancer Institute (NCI) Central Institutional Review Board. NCI Website. 2020. https://www.ncicirb.org/announcements/frequently-asked-questions-regarding-covid-19-and-cirb. Department of Health & Human Services.; Cancer Therapy Evaluation Program (CTEP) Website. 2020. https://ctep.cancer.gov/content/docs/Memorandum_on_Interim_Guidance_for_Clinical_Trial_Activities_Affected_by_the_Novel_Coronavirus-3-13-2020.pdf.

ASCO Guidelines for Clinical Trials

- Manage current patients based on sponsor policies and in accord with agency guidance
- Continue treatment on protocol, if possible, maintaining good clinical practice
- Consult sponsor and IRB (Institutional Review Board) with inquiries regarding deviations from protocol requirements during pandemic
- Protocol monitoring modifications may include all study monitoring being virtual visits if the trial sponsor agrees
- Ensure access to drugs prior to patient visit scheduling
- Resume screening and enrollment with consideration to COVID-19 exposure; testing may be appropriate
- Expand access to clinical trial enrollment as imaging, surgery, and ability to collect biospecimens expand safely for patients and staff
- Consider discussion with sponsor regarding eliminating nonessential tests needed for study enrollment and remote laboratory testing
- Contact Principal Investigator and/or trial sponsor to discuss anticipated protocol deviations during the pandemic

ASCO. American Society of Clinical Oncology. 2020.
https://www.asco.org/sites/new-www.asco.org/files/content-files/2020-ASCO-Guide-Cancer-COVID19.pdf.

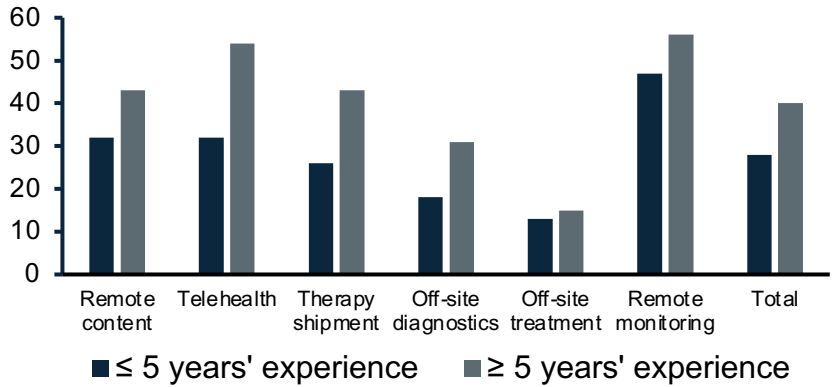
Clinical Trials in LC During COVID-19

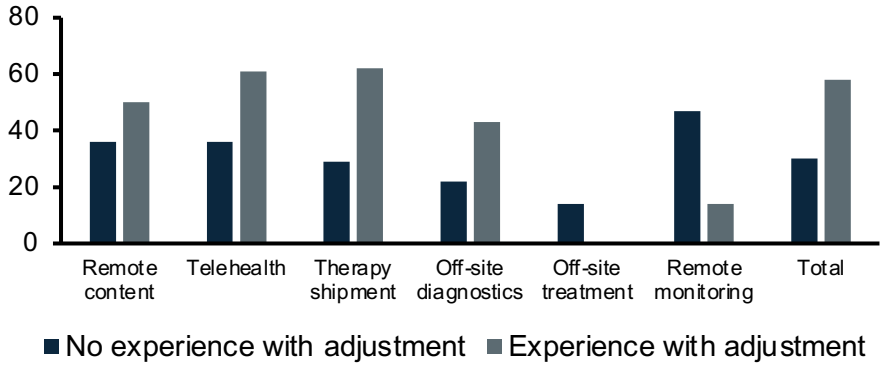
- Enrollment for clinical trials have dropped significantly

Changes in enrollment by patient and trial characteristics and by spread of COVID-19

Characteristic	No. / Total No. (%)			OR (95%CI)	*P* Value
	All Enrolled Patients	Patients Enrolled Weeks 1-11	Patients Enrolled Weeks 12-17		
Research setting					
Treatment	1316/1870 (70.4)	948/1431 (66.2)	368/439 (83.8)	1 [Reference]	NA
Cancer control and prevention	554/1870 (29.6)	483/1431 (33.8)	71/439 (16.2)	0.38 (0.29-0.50)	< .001

- Clinical research professional's perception on clinical trial adjustment is dependent on experience

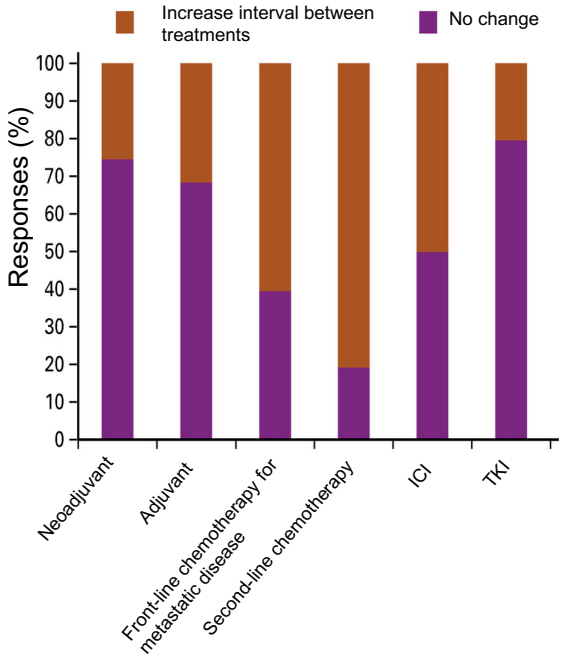


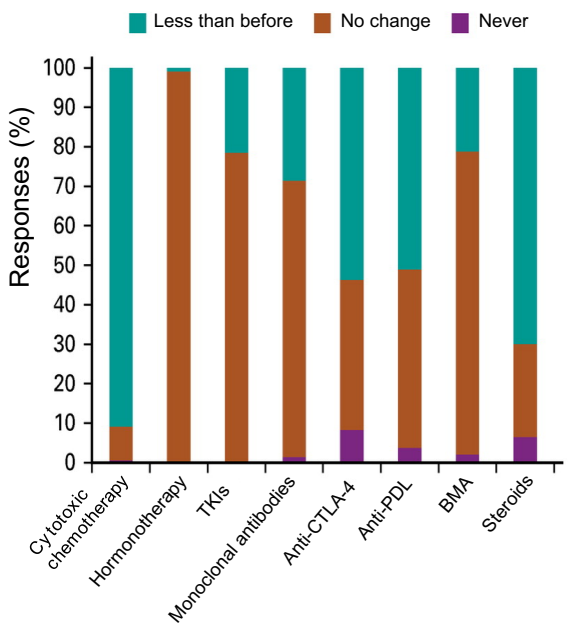


Unger JM, et al. *JAMA Network Open*. 2020;3(6):e2010651.; Gerber DE, Sheffield TY. *JNCCN*. 2020;1-8.

Impact of COVID-19 on Oncology Practice

- Effect of COVID-19 on treatment decisions
  - Definitely (61%)
  - Probably/Possibly (36%)
  - Probably/Definitely not (4%)
- Factors affecting systemic therapy
  - Age of patient (81%)
    Comorbidities (92%)
- Use of G-CSF
  - Increased 78%
  - No change 22%
- Telemedicine usage
  - Yes 80%





BMA = bone-modifying agents; ICI = immune checkpoint inhibitor; TKI = tyrosine kinase inhibitor

Ürün Y, et al. *JCO Global Oncol*. 2020(6):1248-1257.

TERAVOLT: Assessing Thoracic Cancer Patients with COVID-19

- Initial data from a cohort of 200
- 152 (76%) patients were hospitalized and 66 (33%) died
- Death was mainly due to COVID-19 complications
- Anti-cancer treatment did not affect fatality
- 151 (76%) patients with NSCLC

Factors Associated with Death

	Odds Ratio (95% CI)
COPD	1.18 (0.59-2.37)
Hypertension	1.16 (0.61-2.21)
Female sex (vs. male)	0.69 (0.33-1.44)
Age > 65 (vs. ≤ 65)	1.53 (0.77-3.03)
Current or former smoker (vs. never smoker)	3.18 (1.11-9.06)
Outcome includes death during hospitalization, in the intensive care unit, or at home	

Garassino MC, et al. *Lancet Oncol*. 2020;21(7):914-922.

Treating NSCLC During COVID-19: Medical Oncology

Stages I/II	Stage III	Stage IV
Neoadjuvant chemotherapy (enabling deferral of surgery by 3 months) in clinical stage II	Stage III NSCLC should receive high priority	Consider all available treatment options for newly diagnosed metastatic NSCLC
Role of adjuvant chemotherapy at the present time should be reconsidered	Guaranteeing subsequent use of durvalumab within 42 days after CT/RT completion	ICI schedule modified/delayed to reduce clinical visit, using 4-weekly nivolumab 480 mg or 6-weekly pembrolizumab 400 mg instead of the standard 2-weekly or 3-weekly
Use of granulocyte growth factors in adjuvant or neoadjuvant platinum-based chemotherapy	Use of granulocyte growth factors in high febrile neutropenia risk (10%-15%)	TKIs in oncogene-driven NSCLC must continue unaltered

Passaro A, et al. *ESMO Open*. 2020;5(Suppl 3):e000820.

Use of Telemedicine in Patients with Lung Cancer

- Worldwide backlog of surgeries due to COVID-19
- Significant upsurge in the use of telemedicine
- ESMO recommendations for use of telemedicine in patients with lung cancer
  - All non-priority patient appointments
  - Non-urgent situations for established patients without new complaints
  - Patients on long-term follow-up with low/intermediate risk of relapse
- ASCO also has detailed guidelines for use of telemedicine in cancer care

McCall B. *The Lancet Digital Health*. 2020;2(9):e456-e457. Passaro A, et al. *ESMO Open*. 2020;5(Suppl 3):e000820.
ASCO Website. 2020. https://www.asco.org/sites/new-www.asco.org/files/content-files/2020-ASCO-Guide-Cancer-COVID19.pdf.

Discussion Points

- How has COVID-19 impacted your practice?
- How do you convey prognosis?
- How do you explain disease progression when you cannot share scanned images?

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Apply predictive biomarkers to determine appropriate treatment
- Utilize liquid biopsy and NGS for molecular diagnosis
- Evaluate complexities, challenges, and potential of ADCs for NSCLC
- Modify treatment plans to deliver cancer care during the COVID-19 pandemic

CME Outfitters

AFTER THE SHOW

Questions & Answers
Recorded on December 2, 2020

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