UNC LINEBERGER COMPREHENSIVE CANCER CENTER

# Lung Cancer Management in North Carolina: Updates for 2022

**March 23, 2022**

1

## Disclosures

No relevant disclosures

2

## Learning Objectives

- Describe the importance of comprehensive biomarker testing for treatment decisions in non-small cell lung cancer
- Recognize biomarkers for recently approved therapies for lung cancer
- Describe the role of immune checkpoint blockade in resectable lung cancer

3

## Outline

- Overview of molecular testing approaches
- Recent targeted therapy approvals for NSCLC
  - KRAS G12C mutation
  - EGFR exon 20 insertion mutations
- Immune checkpoint blockade for resectable NSCLC

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

4

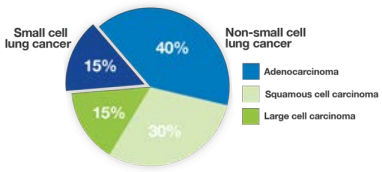
## Case

- BT is a 70-year-old female non-smoker with a PMH of hypertension who presents to her PCP with left neck swelling for 2 weeks
- CT scan of the neck reveals supraclavicular lymphadenopathy
- CT scan of the chest demonstrates a dominant left upper lobe mass with mediastinal lymph node enlargement and bilateral lung nodules
- She is referred to interventional radiology and a core biopsy of the supraclavicular mass is performed
- Pathology: non-small cell carcinoma consistent with lung adenocarcinoma (CK-7, TTF-1 and Napsin positive)

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

5

## Lung Cancer: Histologic Subtypes

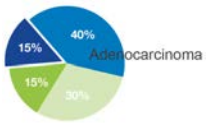



https://lcfamerica.org/lung-cancer-info/types-lung-cancer/

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

6

## Genomic profiling methods

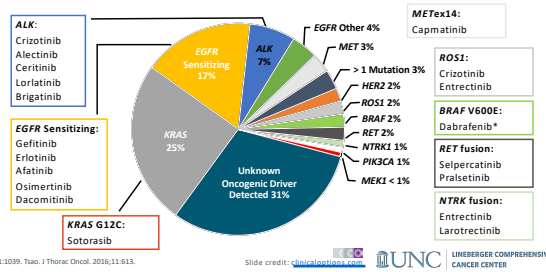



- Tissue-based:
  - Next Generation Sequencing (DNA or RNA)
  - Polymerase chain reaction (PCR)
  - Fluorescence in situ hybridization (FISH)
  - Immunohistochemistry (IHC)
- Blood-based ("liquid biopsy")

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

7

## Advanced Nonsq NSCLC can have Driver Mutations Targetable by an FDA-Approved Agent




Li. JCO 2013;31:1039. Tsao. J Thorac Oncol. 2016;11:613.

Slide credit: clinicaloptions.com

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

8

## Case

- Biopsy specimen is submitted for DNA-based next generation sequencing but there is insufficient material
- A "liquid biopsy" assay is performed
- A KRAS G12C mutation is identified by cfDNA analysis
- Immunohistochemistry with the PD-L1 22C3 assay demonstrates a tumor proportion score (TPS) of 20%
- What therapy choices does this patient have?

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

9

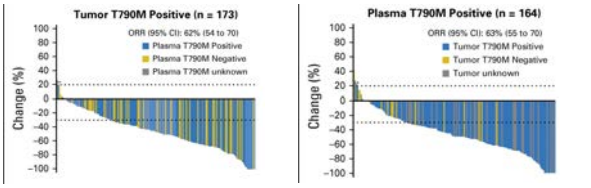
## Concordance of blood and tissue-based testing

- Variable sensitivity (60-90%)
- High concordance with tissue testing for driver mutations
- Longitudinal analysis, resistance mechanisms
- Challenges:
  - Subclonal mutations
  - Clonal hematopoiesis of indeterminate potential (CHIP)
  - Identifying fusions

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

10

## Treatment outcomes by plasma mutation



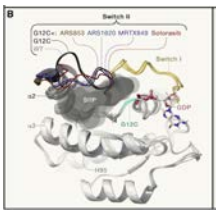

Oxnard GR et al. *J Clin Oncol*, 2016.

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

11

## KRAS Mutations

- *KRAS* G12C ~ 13% lung adenocarcinomas
- Irreversible, $KRAS^{G12C}$ specific inhibitors
- Bind inactive, GDP-bound state



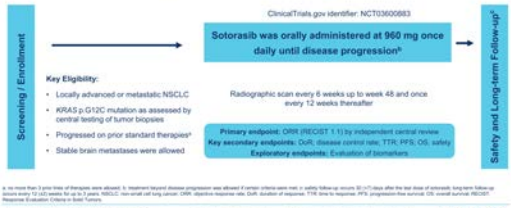

Kim D, Xue JY, Lito P. *Cell*, 2020

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

12

## CodeBreaK 100: Sotorasib

### Phase 2 CodeBreaK100 Trial Design




Skoulidis F et al. *ASCO Annual Meeting*, 2021

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

13

## Sotorasib: Efficacy

| Outcome | Sotorasib 960 mg QD (N = 124) |
|---|---|
| Confirmed ORR, % (95% CI)* | 37.1 (28.6-46.2) |
| ▪ CR, n (%) | 4 (3.2) |
| ▪ PR, n (%) | 42 (33.9) |
| ▪ SD, n (%) | 54 (43.5) |
| ▪ PD, n (%) | 20 (16.1) |
| ▪ Not evaluable or missing scan, n (%) | 4 (3.2) |
| DCR, % (95% CI) | 80.6 (72.6-87.2) |
| Median DoR, mo (95% CI) | 11.1 (6.9-NE) |
| Median TTR, mo (range) | 1.35 (1.2-10.1) |
| Median PFS, mo (95% CI) | 6.8 (5.1-8.2) |

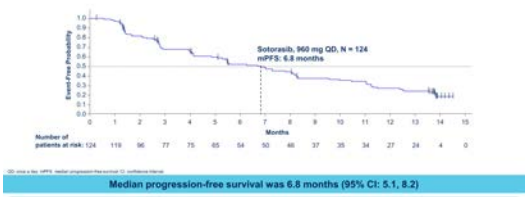
Skoulidis F et al. *ASCO Annual Meeting*, 2021.
Skoulidis F et al. *N Engl J Med*, 2021.

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

14

## CodeBreaK 100: Sotorasib

### Progression-Free Survival



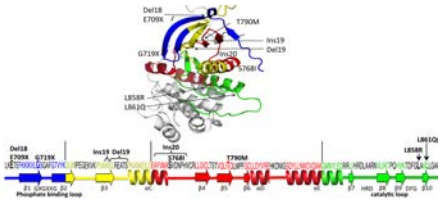

Median progression-free survival was 6.8 months (95% CI: 5.1, 8.2)

Skoulidis F et al. *ASCO Annual Meeting*, 2021

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

15

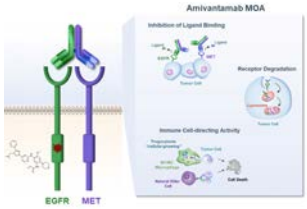
## Not all EGFR mutations are the same: Exon 20 insertion



16

## Amivantamab: post-platinum EGFR exon 20 insertion mutant

- Fully human EGFR-MET bispecific antibody
- Exon 20 insertion mutations insensitive to EGFR TKIs
- 3rd most common EGFR mutation




17

## CHRYSALIS: Amivantamab in Postplatinum Advanced NSCLC With *EGFR* Exon 20 Insertion Mutations

- Dose-escalation/expansion phase I trial of amivantamab, an EGFR-MET bispecific antibody

Patients with unresectable/metastatic NSCLC with an *EGFR* ex20ins mutation who progressed on prior platinum-based chemotherapy (N = 460)

**Dose-Escalation Cohorts, All With Advanced NSCLC**

**Amivantamab** 140-1750 mg on Day 1, Day 8, then Q2W

**Dose-Expansion Cohort D, *EGFR* Ex20ins**

**Amivantamab** at RP2D (1050 mg (<80 kg) or 1400 mg (≥80 kg)) on Day 1, Day 8, then Q2W

*Median follow-up: 9.7 mo (range: 1.1-29.3 mo)*

**Safety Population**
Postplatinum ex20ins treated at RP2D (N = 114)

**Efficacy Population**
Postplatinum ex20ins with ≥3 disease assessments at clinical cutoff (n = 81)

- **Primary endpoint:** ORR (per RECIST v1.1), CBR, DoR, AEs (per CTCAE v4.03)
- **Secondary endpoints:** PFS, OS, PK, and immunogenicity

Sabari. WCLC 2020. Abstr OA04.04. NCT02609776. Park. JCO. 2021;[EPub].

18

IASLC 2020 World Conference on Lung Cancer Singapore

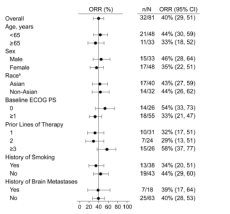
wclc2020.IASLC.com | #WCLC20

CONQUERING THORACIC CANCERS WORLDWIDE

## Amivantamab: Efficacy by BICR

| BICR-assessed Response | Efficacy Population (n=81) |
|---|---|
| Overall response rate | **40%** (95% CI, 29–51) |
| Median duration of response | **11.1 months** (95% CI, 6.9–NR) |
| Best response, n (%) | |
| Complete response | 3 (4) |
| Partial response | 29 (36) |
| Stable disease | 39 (48) |
| Progressive disease | 8 (10) |
| Not evaluable | 1 (1) |
| Clinical benefit rate[a] | 74% (95% CI, 63–83) |

Median follow-up: 9.7 months (range, 1.1–29.3)

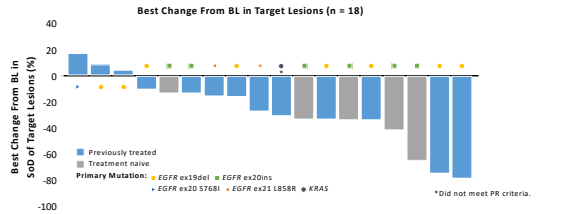



8 October 2020 efficacy data cut. [a]Clinical benefit rate (CBR) defined as complete response or partial response or stable disease for at least 2 disease assessments. [b]Does not include 9 patients with race not reported and multiple race BICR, blinded independent central review; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; NR, not reached; ORR, overall response rate

Saban JK et al. Phase 1 CHRYSALIS Study in Exon20ins NSCLC #3031 JANUARY 28-31, 2021 | WORLDWIDE VIRTUAL EVENT

19

## **CHRYSALIS:** Efficacy of Amivantamab + Chemotherapy



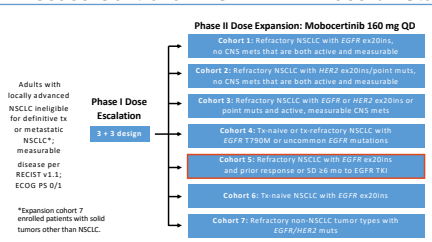

- 80% of treatment-naive patients (n = 5) with *EGFR* ex20ins mutations had a best response of PR and remained on treatment at the time of this analysis

Nagasaka. WCLC 2021. Abstr P50.04.

UNC Slide 3 of 3 UNC LINEBERGER COMPREHENSIVE CANCER CENTER

20

## Mobocertinib in *EGFR* ex20ins+ NSCLC With PD After Disease Control on EGFR TKI: Phase I/II Study Design




**EXCLAIM Extension Cohort: previously treated advanced NSCLC with *EGFR* ex20ins**

**Current analysis:**

- Patients with refractory *EGFR* ex20ins+ metastatic NSCLC with disease progression after response or SD for ≥6 mo on prior EGFR TKI therapy (n = 20)
  - Data cutoff: November 1, 2020
  - Median f/u: 14.2 mo (range: 5.2-21.2)

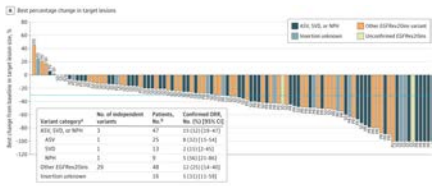
- **Primary endpoint (phase II):** ORR by RECIST v1.1
- **Select secondary endpoints (phase II):** ORR by IRC, BOR, DCR, DoR, TTR, PFS, OS, safety/tolerability

Soria. WCLC 2021. Abstr OA15.01. Zhou. JAMA Oncol. 2021;[Epub]. Riely. Cancer Discov. 2021;11:1688. NCT02716116.

UNC Slide 3 of 3 UNC LINEBERGER COMPREHENSIVE CANCER CENTER

21

## Mobocertinib: Platinum Pretreated



Zhou C et.al *JAMA Oncol*, 2021.

22

## Mobocertinib in *EGFR* ex20ins+ Advanced NSCLC With PD After Disease Control on EGFR TKI: Response

| Response | Cohort 5 (n = 20) |
|---|---|
| Investigator-assessed ORR,* % (95% CI) | 20 (19.1-63.9) |
| Confirmed ORR, % (95% CI) | 40 (19.1-63.9) |
| ▪ PR | 8 (40) |
| ▪ SD | 10 (50) |
| Confirmed ORR on mobocertinib by prior TKI, n/N (%) | |
| ▪ Poziotinib | 4/13 (31) |
| ▪ Osimertinib | 2/4 (50) |
| ▪ Afatinib | 1/4 (25) |
| ▪ Erlotinib | 1/2 (50) |
| ▪ Investigational TKI | 1/1 (100) |
| Confirmed DCR per investigator, n (%) | 18 (90) |
| Median DoR, mo (95% CI) | 13.0 (5.6-13.5) |

*Primary endpoint

Spira. WCLC 2021. Abstr OA15.01.

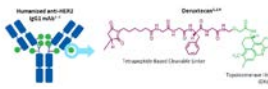
23

## Question 1

- Which of the following genomic alterations do NOT currently have FDA approved therapies for NSCLC?
- MET exon 14 deletion
- KIF5B-RET fusion
- KRAS G12D
- ROS1

24

## HER2 activating mutations



- HER2-activating mutations in 1-3% of NSCLC
- Trastuzumab deruxtecan is a HER2-antibody drug conjugate

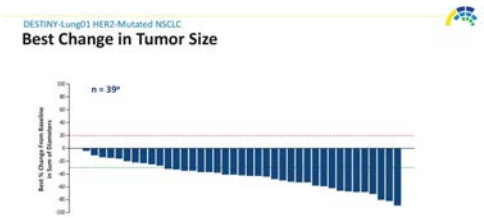
| | Patients (N = 42) |
|---|---|
| Confirmed ORR by ICR | 61.9% (n = 26) (95% CI, 45.6%-76.4%) |
| CR | 2.4% (n = 1) |
| PR | 59.5% (n = 25) |
| SD | 28.6% (n = 12) |
| PD | 4.8% (n = 2) |
| Not evaluable | 4.8% (n = 2) |
| Disease control rate | 90.5% (95% CI, 77.4%-97.3%) |
| Duration of response,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

Smith EF et al. ASCO, 2020

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

25

## DESTINY-Lung 01

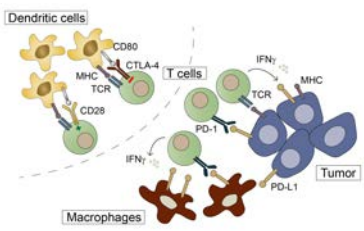



Smith EF et al. ASCO, 2020

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

26

## Immunotherapy: Mechanism of Action




Patel, SA and Weiss JM. *Clin Chest Med*, 2020.

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

27

## Biomarkers: Immunotherapy

- PD-L1 Immunohistochemistry (IHC)
  - IHC is fast and readily available
  - Tumor proportion score (TPS): percentage of tumor cells showing positive staining
  - Concordance between antibodies and samples
- Tumor mutational burden (TMB)

Tsao, MS et al. *J Thorac Oncol*, 2018

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

28

## Immunotherapy agents

| PD-1 antibodies: | **PD-L1 antibodies**: | **CTLA-4 antibodies:** |
|---|---|---|
| Pembrolizumab | Atezolizumab | Ipilimumab |
| Nivolumab | Durvalumab | Tremelimumab |
| Cemiplimab | Avelumab | |

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

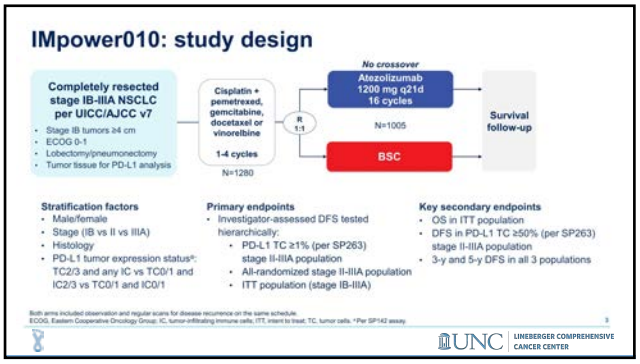
29

## Question 2

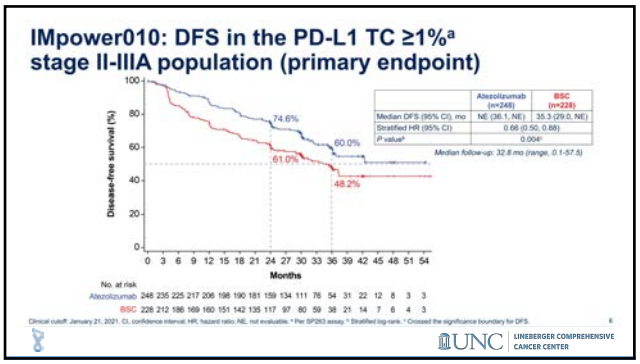
- Which biomarkers are used to select NSCLC patients for immune checkpoint blockade?
  - PD-L1 Immunohistochemistry
  - T-cell inflamed gene expression profile
  - Mismatch repair deficiency
  - EGFR mutations

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

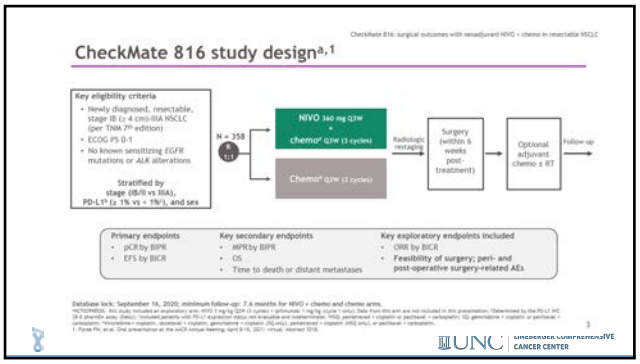
30


IMpower010: study design
Completely resected stage IB-IIIA NSCLC per UICC/AJCC v7
Stage IB tumors ≥4 cm
ECOG 0-1
Lobectomy/pneumonectomy
Tumor tissue for PD-L1 analysis
Cisplatin + pemetrexed, gemcitabine, docetaxel or vinorelbine
1-4 cycles
N=1280
R 1:1
No crossover
Atezolizumab 1200 mg q21d 16 cycles
N=1005
BSC
Survival follow-up
Stratification factors
Male/female
Stage (IB vs II vs IIIA)
Histology
PD-L1 tumor expression status: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1
Primary endpoints
Investigator-assessed DFS tested hierarchically:
PD-L1 TC ≥1% (per SP263) stage II-IIIA population
All-randomized stage II-IIIA population
ITT population (stage IB-IIIA)
Key secondary endpoints
OS in ITT population
DFS in PD-L1 TC ≥50% (per SP263) stage II-IIIA population
3-y and 5-y DFS in all 3 populations
UNC LINEBERGER COMPREHENSIVE CANCER CENTER

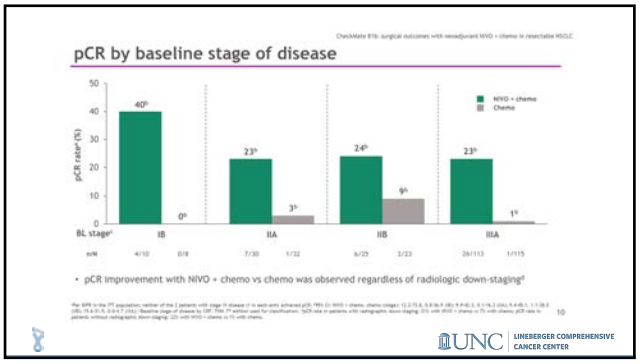
31


IMpower010: DFS in the PD-L1 TC ≥1%a stage II-IIIA population (primary endpoint)
Disease-free survival (%)
Months
74.6%
60.0%
61.0%
48.2%
Atezolizumab (n=248)
BSC (n=228)
Median DFS (95% CI), mo
NE (36.1, NE)
35.3 (29.0, NE)
Stratified HR (95% CI)
0.66 (0.50, 0.88)
P value
0.004
Median follow-up: 32.8 mo (range, 0.1-57.5)
No. at risk
Atezolizumab 248 235 225 217 206 196 190 181 159 134 111 76 54 31 22 12 8 3 3
BSC 228 212 186 169 160 151 142 135 117 97 80 59 38 21 14 7 6 4 3
UNC LINEBERGER COMPREHENSIVE CANCER CENTER

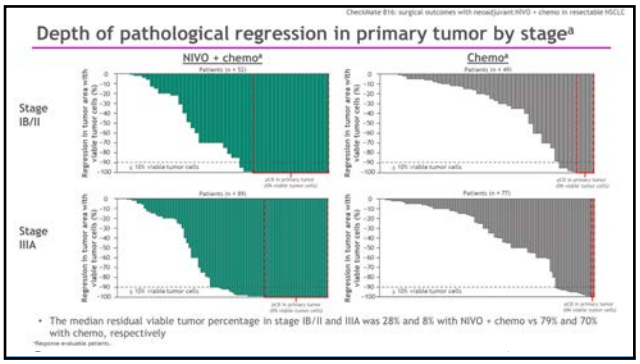
32


CheckMate 816 study design
Key eligibility criteria
Newly diagnosed, resectable, stage IB (≥ 4 cm)-IIIA NSCLC (per TNM 7th edition)
ECOG PS 0-1
No known sensitizing EGFR mutations or ALK alterations
Stratified by stage (IB/II vs IIIA), PD-L1 (≥ 1% vs < 1%), and sex
N = 358
NIVO 360 mg Q3W + chemo Q3W (3 cycles)
Chemo Q3W (3 cycles)
Radiologic restaging
Surgery (within 6 weeks post-treatment)
Optional adjuvant chemo ± RT
Follow-up
Primary endpoints
pCR by BIPR
EFS by BICR
Key secondary endpoints
MPR by BIPR
OS
Time to death or distant metastases
Key exploratory endpoints included
ORR by BICR
Feasibility of surgery; peri- and post-operative surgery-related AEs
UNC CANCER CENTER

33




34




35

**Surgical Outcomes in Checkmate 816**

Surgery delay summary[a]

| | All stages | | Stage IB/II | | Stage IIIA | |
|---|---|---|---|---|---|---|
| | NIVO + chemo (n = 149) | Chemo (n = 135) | NIVO + chemo (n = 55) | Chemo (n = 52) | NIVO + chemo (n = 94) | Chemo (n = 83) |
| Patients with delayed surgery,[b,c] n (%) | 31 (21) | 24 (18) | 9 (16) | 13 (25) | 22 (23) | 11 (13) |
| AE | 6 (4) | 9 (7) | 2 (4) | 7 (13) | 4 (4) | 2 (2) |
| Length of delay in surgery, weeks | | | | | | |
| Median (IQR) | 2.0 (0.6-3.0) | 2.4 (1.0-3.7) | 2.1 (0.9-2.9) | 2.1 (1.3-3.4) | 1.9 (0.6-3.0) | 2.6 (0.6-4.9) |
| Of patients with delayed surgery, proportion n (%) with delay of[d] | | | | | | |
| ≤ 2 weeks | 17 (55) | 11 (46) | 4 (44) | 6 (46) | 13 (59) | 5 (46) |
| > 2 and ≤ 4 weeks | 8 (26) | 8 (33) | 4 (44) | 5 (38) | 4 (18) | 3 (27) |
| > 4 and ≤ 6 weeks | 3 (10) | 2 (8) | 0 | 0 | 3 (14) | 2 (18) |
| > 6 weeks | 3 (10) | 3 (12) | 1 (11) | 2 (15) | 2 (9) | 1 (9) |

• Median (IQR) time from last neoadjuvant dose to definitive surgery was 5.3 (4.6-6.0) weeks with NIVO + chemo and 5.0 (4.6-5.9) weeks with chemo for all patients with definitive surgery

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

36

## Question 3

Adjuvant immune checkpoint blockade improves disease free survival in resectable stage II-III non-small cell lung cancer.

- True
- False

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

37

## Summary

- Genomic profiling of lung adenocarcinomas is important for treatment selection
- Recent targeted therapy approvals include agents targeting KRAS G12C and EGFR exon 20
- Immune checkpoint blockade has been approved for select patients with resectable non-small cell lung cancer

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

38

## References


- Hong DS et al. KRAS(G12C) Inhibition with Sotorasib in Advanced Solid Tumors. *N Engl J Med*. 2020 Sep 24;383(13):1207-1217.
- Skoulidis F et al. Sotorasib for Lung Cancers with *KRAS* p.G12C Mutation. N Engl J Med. 2021 Jun 24;384(25):2371-2381.
- Park K et al. Amivantamab in EGFR Exon 20 Insertion-Mutated Non-Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study. J Clin Oncol. 2021 Oct 20;39(30):3391-3402.
- Riely GJ et al. Activity and Safety of Mobocertinib (TAK-788) in Previously Treated Non-Small Cell Lung Cancer with *EGFR* Exon 20 Insertion Mutations from a Phase I/II Trial.
- Zhou C et al. Treatment Outcomes and Safety of Mobocertinib in Platinum-Pretreated Patients With EGFR Exon 20 Insertion-Positive Metastatic Non-Small Cell Lung Cancer: A Phase 1/2 Open-label Nonrandomized Clinical Trial. JAMA Oncol. 2021 Dec 1;7(12):e214761.
- Smit EF et al. Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients with HER2-Mutated Metastatic Non-Small Cell Lung Cancer: Interim Results of DESTINY-Lung01. *ASCO Annual Meeting*, 2020.
- Patel SA and Weiss J. Advances in the Treatment of Non-Small Cell Lung Cancer: Immunotherapy. *Clin in Chest Med*, 2020 June; 41(2):237-247.
- Felip E et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. Lancet. 2021 Oct 9;398(10308):1344-1357.
- Spicer J et al. Surgical outcomes from the phase 3 CheckMate 816 trial: Nivolumab + platinum-doublet chemotherapy (chemo) vs chemo alone as neoadjuvant treatment for patients with resectable non-small cell lung cancer (NSCLC).

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

39

## Acknowledgements

**Thoracic Medical Oncology**
Jared Weiss, MD
Marjory Charlot, MD, MPH
Chad Pecot, MD
Carrie Lee, MD, MPH
Chaely Medley, NP
Amanda Maddry, RN, BSN
Tammy Allred, RN OCN

**Radiation Oncology**
Ashley Weiner, MD PhD
Larry Marks, MD

**Pulmonary**
Jason Akulian, MD, MPH
Cole Burks, MD
Christina MacRosty, DO
M. Patricia Rivera, MD

**Thoracic Surgery**
Gita Mody, MD
Jason Long, MD
Ben Haithcock, MD

UNC LINEBERGER COMPREHENSIVE CANCER CENTER

40