Targeted Therapy Updates in NSCLC

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Disclosures

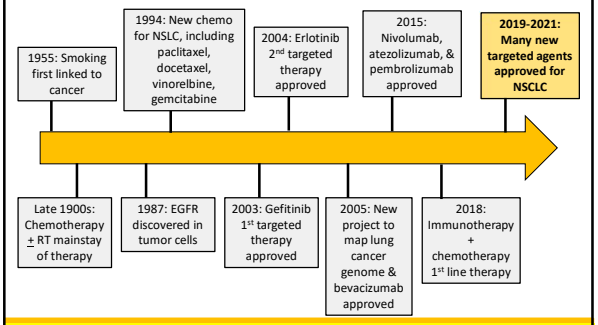
I have nothing to disclose

I will not be discussing off-label indications

Objectives

- Review history of non-small cell lung cancer (NSCLC) treatment and current treatment guidelines
- Discuss new targeted therapies for patients with NSCLC and specific gene mutations
- Optimize patient care by examining drug interactions and monitoring parameters of targeted therapies
- Develop treatment plans for patients with targetable mutations

History of NSCLC Therapy



ASCO. Cancer Progress Timeline. Available at: https://www.asco.org/research-guidelines/cancer-progress-timeline/lung-cancer

NCCN Guidelines

Stage I
Surgery ± RT followed by observation
Consider adjuvant therapy for high risk IB

Stage II
Surgery ± adjuvant therapy

Stage III Resectable
Neoadjuvant therapy + surgery
Surgery + neoadjuvant therapy

Stage III Unresectable
Definitive chemo + RT → immunotherapy

Stage IV
Targeted therapy (if targetable mutation present)
Chemotherapy ± immunotherapy
Immunotherapy alone
Best supportive care

RT = radiation therapy; Chemotherapy = platinum-based doublet

NCCN. Non-Small Cell Lung Cancer. v.5.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

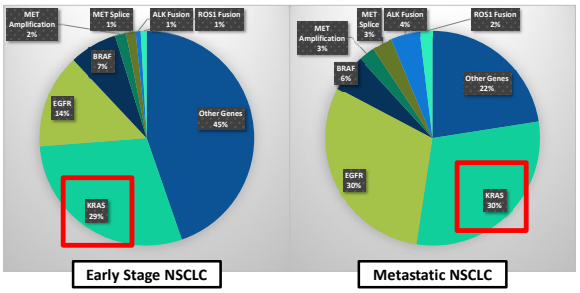
Targeted Therapies

Testing Result	Available Agents*
EGFR mutation (exon 19, L858R)	**Osimertinib,** Afatinib, Dacomitinib, Erlotinib, Gefitinib
EGFR mutation (exon 20 insertion)	**Amivantamab** (2nd line)
KRAS G12C mutation	**Sotorasib** (2nd line)
ALK rearrangement	**Alectinib, Brigatinib, Lorlatinib,** Ceritinib, Crizotinib
ROS1 rearrangement	**Entrectinib, Crizotinib,** Ceritinib, Entrectinib, Lorlatinib
BRAF V600E mutation	**Dabrafenib + Trametinib,** Vemurafenib
NTRK 1/2/3 gene fusion	**Entrectinib, Larotrectinib**
METex14 skipping mutation	**Capmatinib, Tepotinib,** Crizotinib
RET rearrangement	**Pralsetinib, Selpercatinib,** Cabozantinib, Vandetanib

***bolded agents preferred by NCCN guidelines**

NCCN. Non-Small Cell Lung Cancer. v.5.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

Oncogenic Drivers



Skoulidis F, et al. *Nature Reviews*. 2019;19:495-509.

KRAS Mutation

- Kirsten Rat Sarcoma (KRAS) oncogene
- Predominantly adenocarcinoma with smoking-related mutations
- Associated with resistance to targeted therapies & poor outcomes
- Most frequent KRAS mutations account ~83% of mutations
  - G12D, G12V, G13D, G12C
- KRAS p.G12C mutation occurs in ~ 13% of NSCLC
  - ***Significantly decreased disease free survival (DFS) and overall survival (OS)***

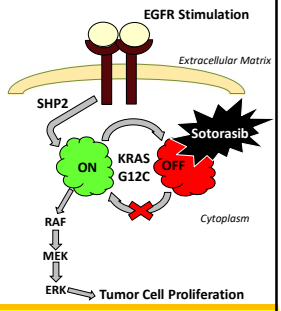
Nadal E, et al. *J Thorac Oncol*. 2014;9:1513-1522.
Stolze B, et al. *Sci Rep*. 2015;5:8535.

KRAS Mutation

Sotorasib (Lumakras®)
Forms covalent irreversible bond with unique cysteine of **KRAS G12C** & locks protein in inactive state

FDA-approved May 2021

For KRAS G12C mutation + NSCLC after progression on platinum doublet chemo +/- immunotherapy



Skoulidis F, et al. *N Engl J Med*. 2021;384:2371-2381.
Lumakras (sotorasib) [package insert]. Thousand Oaks, CA: Amgem Inc.; 021.

CodeBreaK 100 Trial

Methods
- Single group, phase 2 trial
- Sotorasib 960 mg by mouth once daily

Inclusion Criteria
- Age ≥ 18
- Locally advanced or metastatic NSCLC + **KRAS p.G12C** mutation + disease progression after platinum-based chemotherapy ± immunotherapy
- ECOG 0 – 1
- Measurable disease according to RECIST

Exclusion Criteria
- Active untreated brain metastases
- > 3 previous lines of therapy
- Systemic anticancer therapy within 28 days prior to sotorasib
- Radiation therapy within 2 weeks prior to sotorasib
- Previous treatment with direct KRAS G12C inhibitor

ECOG = Eastern Cooperative Oncology Group; RECIST = Response Evaluation Criteria in Solid Tumors

Skoulidis F, et al. *N Engl J Med*. 2021;384:2371-2381.

CodeBreaK 100 Patients

Baseline Characteristics	Patients (N = 126)
Median Age, yrs	63.5
Female	50
Race	
White	81.7
Asian	15.1
Black	1.6
Current Smoker	11.9
Former Smoker	81
ECOG 1	69.8
Adenocarcinoma	95.2

Baseline Characteristics	Patients (N = 126)
Metastatic Disease	96.8
Brain Metastasis	20.6
Previous Lines of Therapy	
1	42.9
2	34.9
3	22.2
Type of Previous Therapy	11.9
Platinum Chemo	89.7
Immunotherapy	91.3 – 92.1
Combination	81

No. % unless otherwise stated

Skoulidis F, et al. *N Engl J Med*. 2021;384:2371-2381.

CodeBreaK 100 Results

Primary Endpoint	Patients (N = 124)
Objective Response (complete or partial)	37.1%

Secondary Endpoints	Patients (N = 124)
Disease Control	100 (80.6%)
Median Duration of Response	11.1 months
Median PFS	6.8 months
Median OS	12.5 months

Best Response, %	Patients (N = 124)
Complete Response	3.2
Partial Response	33.9
Stable Disease	43.5
Progressive Disease	16.1

Kaplan-Meier Estimate for Objective Response	Patients (N = 124)
At 3 months	90.5%
At 6 months	70.8%
At 9 months	57.3%

PFS = progression free survival; OS = overall survival

Skoulidis F, et al. *N Engl J Med*. 2021;384:2371-2381.

CodeBreaK 100 Safety Outcomes

Treatment-Related Adverse Event, %	Any Grade	Grade 1/2	Grade 3	Grade 4	Grade 5
Any	69.8	49.2	19.8	0.8	0
Diarrhea	31.7	27.8	4	0	0
Nausea	19	19	0	0	0
ALT Increase	15.1	8.7	6.3	0	0
AST Increase	15.1	9.5	5.6	0	0
Fatigue	11.1	11.1	0	0	0
Dyspnea	1.6	0.8	0	0.8	0
Pneumonitis	1.6	0	0.8	0.8	0
Leading to Dose Modification	22.2	6.3	15.9	0	0
Leading to Discontinuation	7.1	3.2	3.2	0.8	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase

Skoulidis F, et al. *N Engl J Med*. 2021;384:2371-2381.

Sotorasib Pearls

Administration

- Sotorasib 960 mg by mouth daily
- Available as 120 mg tablets = 8 tablets required daily
- Administer ± food

Monitoring Parameters

- LFTs prior to therapy, every 3 weeks x 3 months, then monthly or as indicated
- AEs: diarrhea, nausea, skin rash, pneumonitis
- Adherence

Drug Interactions

- CYP3A4: major substrate & moderate inducer
- Avoid acid-reducing agents (choose H2RA if unable to be avoided)

LFTs = liver function tests; AEs = adverse events; H2RA = H_2 receptor antagonist

Lumakras (sotorasib) [package insert]. Thousand Oaks, CA: Amgem Inc.; 2021.

Patient Case

- KM is a 72-year-old male
- Diagnosed with stage IVA NSCLC adenocarcinoma with liver + bone metastases during August 2021
- He still has good performance status (ECOG 1)

What treatment should KM receive for his recurrent disease?

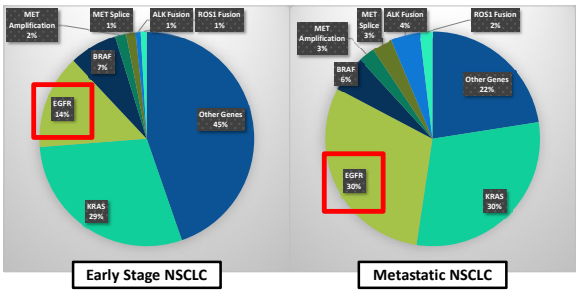
What is the best treatment plan for KM's newly diagnosed stage IVA NSCLC adenocarcinoma?

A. Platinum-based chemoradiation
B. Neoadjuvant platinum-based chemotherapy + surgery
C. Check molecular testing prior to starting any therapy
D. Initiate immunotherapy right away

Results of molecular testing demonstrate positive KRAS G12C mutation and PD-L1 is 0%. What is the best treatment plan for KM at this time?

A. Sotorasib 960 mg daily
B. Osimertinib 80 mg daily
C. Pembrolizumab + carboplatin + pemetrexed
D. None of the above

Oncogenic Drivers



Skoulidis F, et al. *Nature Reviews*. 2019;19:495-509.

EGFR Mutation

- Epidermal growth factor receptor (EGFR)
- Transmembrane protein important for growth factor signaling from extracellular matrix to the cell
- Primarily adenocarcinoma with minimal or no smoking history
- Important activating mutations:
  - Exon 19 deletion (Ex19del)
  - Exon 21 substitution (L858R)

  } 85 – 90% of TK domain mutations
  - T790M → approximately 50 – 60% of acquired resistance to EGFR therapy
  - Exon 20 insertion → 9 – 12% of EGFR mutations in NSCLC

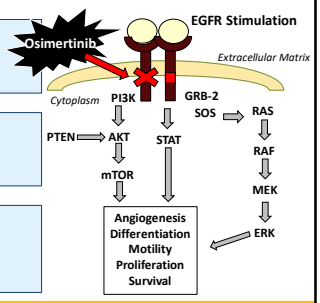
Guo MZ, et al. *touchREVIEWS.* 2021;17(1):42-7.
Santos GC, et al. *Annu. Rev. Pathol. Mech. Dis.* 2011;6:49-69.

EGFR Ex19del, L858R, T790M Tyrosine Kinase Inhibitors (TKIs)

1st Generation
- Drugs: erlotinib, gefitinib
- Reversible
- Targets wild-type EGFR & mutations

2nd Generation
- Drugs: afatinib, dacomitinib
- Irreversible
- Targets wild-type EGFR & mutations

3rd Generation
- Drug: osimertinib
- Irreversible, potent, CNS-active
- More selective for EGFR mutations, including T790M resistance mutation



Ahluwalia MS, et al. *The Oncologist.* 2018;23:1199-1209.
Santos GC, et al. *Annu. Rev. Pathol. Mech. Dis.* 2011;6:49-69.

ADAURA Trial

Methods
- Double-blind, placebo-controlled, randomized, international phase 3 trial
- 1:1 ratio → adjuvant osimertinib 80 mg by mouth once daily vs. placebo x 3 years or until disease recurrence or toxicity
- Administration of standard post-op adjuvant chemotherapy before randomization permitted but not mandatory

Inclusion Criteria
- Age ≥ 18 (in Japan & Taiwan ≥ 20)
- Primary non-squamous NSCLC with postsurgical pathological stage IB, II, or IIIA
- EGFR mutation (Ex19del, L858R)
- WHO performance status 0 – 1
- Complete recovery from surgery with randomization between 4 – 10 weeks post-op without adjuvant chemo or 4 – 26 weeks post-op + adjuvant chemo

Exclusion Criteria
- Surgery only segmentectomies or wedge resections
- Radiation therapy at any time point for current lung cancer
- Any previous therapy other than standard platinum-based doublet adjuvant chemo
- Previous treatment with neoadjuvant or adjuvant EGFR-TKI
- Several other standard exclusion criteria (drug interactions, organ function, etc.)

WHO = World Health Organization

Wu Y, et al. *N Engl J Med.* 2020;383:1711-23.

ADAURA Patients

Baseline Characteristics	Patients (N = 682)
Median Age, yrs	62 – 64
Female	70
Asian Race	64
Never Smoker	70
Median Pack-Year for Smokers, pk-yr	20
WHO 0	64
Lobectomy	95
Adjuvant Chemotherapy	60

Baseline Characteristics	Patients (N = 682)
Adenocarcinoma	97
EGFR Mutation	
ex19del	55
L858R	45
pThr790Met	1
Stages (IB, II, IIIA)	Each ~ 30
Regional Lymph Nodes N0	40

No. % unless otherwise stated

Wu Y, et al. *N Engl J Med.* 2020;383:1711-23.

ADAURA Results

Primary Endpoint	Patients (N = 682)
DFS in stage II - IIIA	90% osimertinib vs. 44% placebo (HR 0.17, p < 0.001)

Secondary Endpoints	Patients (N = 682)
DFS in overall population stage IB - IIIA	89% osimertinib vs. 52% placebo (HR = 0.2, p < 0.001)
Median CNS DFS	90% osimertinib vs. 85% placebo alive without CNS disease (HR = 0.17, 95% CI 0.10 – 0.33)
DFS with Adjuvant Chemo	89% osimertinib vs. 49% placebo (HR = 0.16, 95% CI 0.10 – 0.26)
DFS without Adjuvant Chemo	89% osimertinib vs. 58% placebo (HR = 0.23, 95% CI 0.13 – 0.40)

DFS = disease-free survival at 24 months according to investigator assessment

Wu Y, et al. *N Engl J Med.* 2020;383:1711-23.

ADAURA Safety Outcomes

	Osimertinib (N = 337)				Placebo (N = 343)				
Adverse Event, %	Any Grade	Grade 1	Grade 2	Grade 3	Adverse Event, %	Any Grade	Grade 1	Grade 2	Grade 3
Diarrhea	46	34	9	2	Diarrhea	20	16	4	< 1
Paronychia	25	9	15	1	Paronychia	1	1	1	0
Dry Skin	23	22	1	< 1	Dry Skin	6	5	1	0
Pruritus	19	15	5	0	Pruritus	9	8	1	0
Cough	18	13	6	0	Cough	17	12	4	0
Stomatitis	18	10	5	2	Stomatitis	4	3	1	0
Nasopharyngitis	14	9	5	0	Nasopharyngitis	10	7	3	0
URTI	13	7	6	1	URTI	10	6	5	0
Decreased Appetite	13	9	4	1	Decreased Appetite	4	3	1	0
Dermatitis Acneiform	11	9	2	0	Dermatitis Acneiform	5	3	1	0

Wu Y, et al. *N Engl J Med.* 2020;383:1711-23.

URTI = upper respiratory tract infection

Osimertinib Pearls

Administration

- Osimertinib 80 mg by mouth daily up to 3 years
- Available as 40 mg and 80 mg tablets
- Administer ± food

Monitoring Parameters

- QTc prolongation: ECG + electrolytes at therapy initiation then periodically depending on risk factors
- Baseline LVEF prior to treatment then every 3 - 12 months depending on presence of cardiac risk factors
- Pneumonitis (3% with osimertinib compared to 1% with first generation TKIs)
- AEs: diarrhea, skin rash/hand-foot syndrome, pneumonitis, hepatotoxicity, paronychia, stomatitis, ocular toxicity
- Adherence

Drug Interactions

- CYP3A4: major substrate
- P-gp: minor substrate & inhibitor

ECG = electrocardiogram; LVEF = left ventricular ejection fraction; AEs = adverse events; P-gp = P-glycoprotein

Wu Y, et al. *N Engl J Med.* 2020;383:1711-23.
Tagrisso (osimertinib) [package insert]. Wilmington, DE: AstraZeneca; 2020.

Patient Case

- AB is a 62-year-old female
- PMH
  - Former smoker (5-pack yr)
  - COPD
  - Atrial fibrillation (on Xarelto)
  - HTN
  - Dyslipidemia
  - Hypothyroidism
- NSCLC adenocarcinoma
- EGFR exon 19 deletion +
- S/p RML lobectomy with no residual disease
- Stage IB (pT2apN0)

What treatment should AB receive post-resection?

Which of the following is the best course of action for AB's stage IB NSCLC adenocarcinoma post-lobectomy with EGFR exon 19 deletion?

A. No adjuvant therapy recommended for low risk stage IB post-resection

B. Platinum-based chemotherapy followed by observation

C. Osimertinib 80 mg daily until disease progression or unacceptable toxicity indefinitely

D. Osimertinib 80 mg daily until disease progression or unacceptable toxicity for up to 3 years

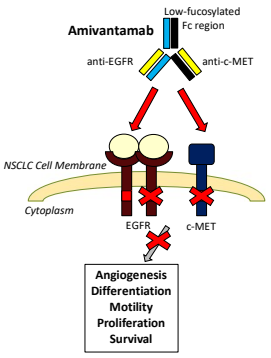
EGFR Exon 20 Insertion

Amivantamab-vmjw (Rybrevant®)
Fully human bispecific antibody targeting EGFR and mesenchymal-epithelial transition (MET)

FDA-approved May 2021

Second-line therapy for NSCLC + EGFR exon 20 insertion mutation

For EGFR exon 20 insertion+ NSCLC after progression on platinum doublet chemo +/- immunotherapy



Guo MZ, et al. *touchREVIEWS in Oncology & Haematology.* 2021;17(1):42-7.
Rybrevant (amivantamab-vmjw) [prescribing information]. Horsham, PA: Janssen Biotech, Inc.; 2021.

CHRYSALIS Trial

Methods
- Phase I, open-label
- Two-part study: dose escalation & dose expansion with treatment until disease progression or toxicity
- Initial data release: amivantamab monotherapy after platinum-based chemotherapy

Inclusion Criteria
- Age ≥ 18
- Metastatic or unresectable NSCLC + EGFR Exon20ins mutation
- Progressed on, ineligible, or declined standard-of-care therapy
- ECOG ≤ 1

Exclusion Criteria
- Previous treatment with investigational EGFR Exon20ins-targeted TKIs in expansion cohort
- Untreated or active brain metastases (unless previously treated and asymptomatic)
- Several other standard exclusion criteria (drug interactions, organ function, etc.)

Park K, et al. *J Clin Oncol.* 2021;JCO2100662.doi: 10.1200/JCO.21.00662

CHRYSALIS Primary Endpoints

- Part 1: Dose Escalation
  - Determine maximum tolerated dose and recommended phase II dose (RP2D)
- Part 2: Dose Expansion
  - Evaluate safety, tolerability, and antitumor activity of amivantamab at RP2D
- Both
  - Incidence of dose-limiting toxicity
  - Overall response rate (ORR)

Park K, et al. *J Clin Oncol.* 2021;JCO2100662.doi: 10.1200/JCO.21.00662

CHRYSALIS Dose Escalation Patients

Baseline Characteristics	Dose Escalation (N = 77)
Median Age, yrs	63
Female	64
Asian Race	62
ECOG 1	71
Non-Smoker	60
Adenocarcinoma	95
Brain Metastases	20
Median Previous Lines of Therapy, no.	3

Previous Systemic Therapy	Dose Escalation (N = 77)
Platinum Chemo	82
Immunotherapy	38
EGFR TKI	77
1st-generation	58
2nd-generation	20
3rd-generation	48
Exon20ins-Targeted Therapy	7
No Previous Therapy	3

No. % unless otherwise stated

Park K, et al. *J Clin Oncol.* 2021;JCO2100662.doi: 10.1200/JCO.21.00662

CHRYSALIS Recommended Phase II Dose (RP2D)

- **Patients < 80 kg**
  - Week 1: 1,050 mg IV split over days 1 and 2 (350 mg day 1 + 700 mg day 2)
  - Weeks 2 – 4: 1,050 mg IV once weekly
  - Subsequent Infusions: 1,050 mg IV once every 2 weeks starting at week 5 until disease progression or unacceptable toxicity
- **Patients ≥ 80 kg**
  - Week 1: 1,400 mg IV split over days 1 and 2 (350 mg day 1 + 1,050 mg day 2)
  - Weeks 2 – 4: 1,400 mg IV once weekly
  - Subsequent Infusions: 1,400mg IV once every 2 weeks starting at week 5 until disease progression or unacceptable toxicity

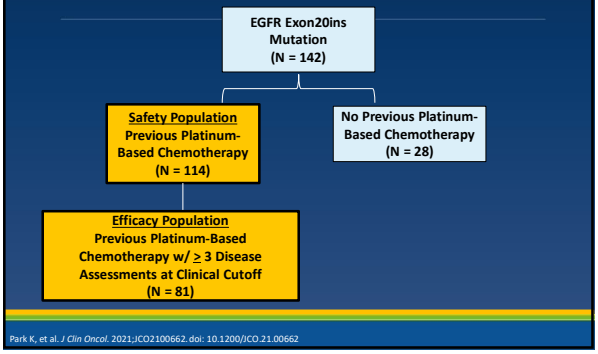
Park K, et al. *J Clin Oncol.* 2021;JCO2100662.doi: 10.1200/JCO.21.00662

CHRYSALIS Dose Expansion (N = 285)

- Cohort A: EGFR-dependent resistance
- Cohort B: EGFR-independent resistance
- Cohort C: Post-EGFR-3GTKI and C797S+
- **Cohort D: EGFR Exon20ins (N = 142)**
- Cohort MET-1: MET amp and post-EGFR-TKI
- Cohort MET-2: MET exon 14 skipping

Park K, et al. *J Clin Oncol.* 2021;JCO2100662.doi: 10.1200/JCO.21.00662

CHRYSALIS Safety & Efficacy Populations



Park K, et al. *J Clin Oncol.* 2021;JCO2100662.doi: 10.1200/JCO.21.00662

CHRYSALIS Dose Expansion Patients

Baseline Characteristics	Efficacy Population (N = 81)
Median Age, yrs	62
Female	59
Asian Race	49
ECOG 1	67
Non-Smoker	53
Adenocarcinoma	95
Brain Metastases	22
Median Previous Lines of Therapy, no.	2

Previous Systemic Therapy	Efficacy Population (N = 81)
Platinum Chemo	100
Immunotherapy	46
EGFR TKI	25
1st-generation	9
2nd-generation	7
3rd-generation	7
Exon20ins-Targeted Therapy	1
No Previous Therapy	0

No. % unless otherwise stated

Park K, et al. *J Clin Oncol.* 2021;JCO2100662.doi: 10.1200/JCO.21.00662

CHRYSALIS Safety Outcomes

Adverse Event (AE), %	Safety Population (N = 114)	Patients Treated at RP2D (N = 258)
Any AE	99	100
Grade ≥ 3	35	39
Serious AE	30	31
AE Leading to Death	7	5
AE Leading to Discontinuation	10	7
AE Leading to Dose Reduction	13	10
AE Leading to Dose Interruption	35	34

RP2D = recommended phase II dose (N = 258 is for all cohorts in dose expansion phase)

Park K, et al. *J Clin Oncol.* 2021;JCO2100662.doi: 10.1200/JCO.21.00662

CHRYSALIS: Safety Population

Adverse Event, %	Any Grade	Grade 1	Grade 2	Grade ≥ 3
Rash	86	38	45	4
Infusion-Related Reaction	66	8	55	3
Paronychia	45	25	19	1
Hypoalbuminemia	27	5	19	3
Constipation	24	16	8	0
Nausea	19	15	4	0
Dyspnea	19	11	7	2
Stomatitis	21	10	11	0
Peripheral Edema	18	18	1	0
Hypokalemia	11	4	1	5

Other AEs with any grade 10-18%: pruritus, fatigue, cough, decreased appetite, dry skin, increased alanine aminotransferase, vomiting, dizziness, myalgia, diarrhea, back pain, pyrexia

Park K, et al. *J Clin Oncol.* 2021;JCO2100662.doi: 10.1200/JCO.21.00662

CHRYSALIS: RP2D Population

Adverse Event, %	Any Grade	Grade 1	Grade 2	Grade ≥ 3
Rash	78	39	36	3
Infusion-Related Reaction	65	8	54	2
Paronychia	40	19	20	1
Hypoalbuminemia	24	8	15	2
Constipation	23	14	9	0
Nausea	21	16	5	0.4
Dyspnea	20	11	5	4
Stomatitis	19	13	7	0
Peripheral Edema	19	17	2	1
Pruritus	19	16	4	0

Other AEs with any grade 10-18%: fatigue, cough, decreased appetite, dry skin, increased alanine aminotransferase, vomiting, dizziness, myalgia, diarrhea, back pain, pyrexia

Park K, et al. *J Clin Oncol.* 2021;JCO2100662.doi: 10.1200/JCO.21.00662

CHRYSALIS Response Outcomes

Response per RECIST, %	Efficacy Population (N = 81)
Overall Response Rate (ORR) [95% CI]	40 [29 – 51]
Clinical Benefit Rate (CBR) [95% CI]	74 [63 – 83]
Best Response	
Complete Response (CR)	4
Partial Response (PR)	36
Stable Disease (SD)	48
Progressive Disease (PD)	10
Not Evaluable (NE)	2

Park K, et al. *J Clin Oncol.* 2021;JCO2100662.doi: 10.1200/JCO.21.00662

Amivantamab Pearls

Administration

- Amivantamab-vmjw IV dosing depends on weight & is slowly titrated up over 4 weeks
- Each vial = 350 mg/7 mL
- Follow specific administration & infusion rates in package insert

Infusion-Related Reactions

- Shortness of breath, flushing, fever, chills, nausea/vomiting, chest pain, hypotension
- ~ 66% of patients will have reaction with 1st dose, incidence drops to ~ 3% with 2nd dose
- Administer pre-medications: antihistamines, antipyretics, glucocorticoids
- Administer via peripheral line week 1 – 2, then via central line permissible

Rybrevant (amivantamab-vmjw) [prescribing information]. Horsham, PA: Janssen Biotech, Inc.; 2021.

Amivantamab Administration Titration 1,050 mg Dose (< 80 kg)

Week	Dose (per 250 mL bag)	Initial Infusion Rate (mL/hour)	Subsequent Infusion Rate* (mL/hour)
Week 1, Day 1	350 mg	50	75
Week 1, Day 2	700 mg	50	75
Week 2	1,050 mg	85	
Week 3	1,050 mg	125	
Week 4	1,050 mg	125	
Subsequent Infusions (dosed every 2 weeks)	1,050 mg	125	

**Increase infusion rate to subsequent infusion rate after 2 hours in absence of infusion-related reactions*

Rybrevant (amivantamab-vmjw) [prescribing information]. Horsham, PA: Janssen Biotech, Inc.; 2021.

Amivantamab Administration Titration 1,400 mg Dose (≥ 80 kg)

Week	Dose (per 250 mL bag)	Initial Infusion Rate (mL/hour)	Subsequent Infusion Rate* (mL/hour)
Week 1, Day 1	350 mg	50	75
Week 1, Day 2	1,050 mg	35	50
Week 2	1,400 mg	65	
Week 3	1,400 mg	85	
Week 4	1,400 mg	125	
Subsequent Infusions (dosed every 2 weeks)	1,400 mg	125	

**Increase infusion rate to subsequent infusion rate after 2 hours in absence of infusion-related reactions*

Rybrevant (amivantamab-vmjw) [prescribing information]. Horsham, PA: Janssen Biotech, Inc.; 2021.

Amivantamab Pearls Continued

Monitoring Parameters

- Infusion-related reactions
- Hypokalemia
- AEs: dermatologic toxicity, photosensitivity, pneumonitis, ocular toxicity

Drug Interactions

- No known interactions at this time

Park K, et al. *J Clin Oncol*. 2021;JCO2100662. doi: 10.1200/JCO.21.00662
Rybrevant (amivantamab-vmjw) [prescribing information]. Horsham, PA: Janssen Biotech, Inc.; 2021.

Which of the following is true about the administration of amivantamab-vmjw?

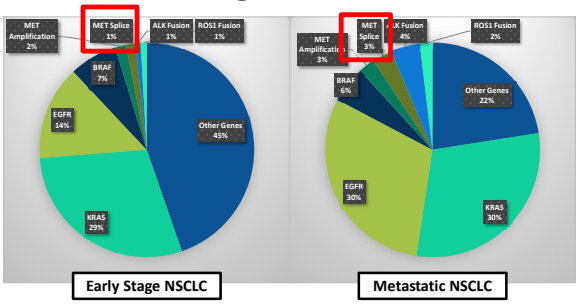
A. Patients are at a high risk of infusion-related reactions during each infusion

B. Amivantamab-vmjw dosing depends on patient's body surface area

C. The dose should be titrated up slowly to prevent infusion-related reactions

D. Pre-medications are not required due to low risk of infusion-related reactions

Oncogenic Drivers



Skoulidis F, et al. *Nature Reviews*. 2019;19:495-509.

MET Exon 14 Skipping Mutation

- Mesenchymal-epithelial transition exon 14 skipping mutation (METex14) is a type of MET splice mutation
- Occurs in both squamous & adenocarcinoma
- More frequent among never-smokers
- Patients typically significantly older than patients with other oncogenic drivers (EGFR, KRAS, ALK)
- Capmatinib (May 2020) and tepotinib (February 2021) are novel agents targeting METex14

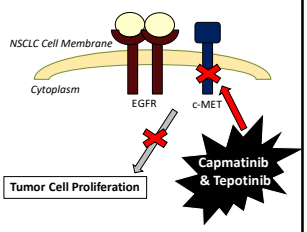
Socinski MA, et al. *J CO Precision Oncology*. 2021;5:653-663.
Santos GC, et al. iAnnu. Rev. Pathol. Mech. Dis. 2011;6:49-69.

MET Exon 14 Skipping Mutation

Capmatinib (Tabrecta) & Tepotinib (Tepmetko®)

Selective TKIs inhibiting MET phosphorylation & downstream signaling pathways

First-line therapy for metastatic NSCLC + METex14 skipping alteration



Socinski MA, et al. *J CO Precision Oncology*. 2021;5:653-663.
Tabrecta (capmatinib) [prescribing information]. East Hanover, NJ; Novartis Pharmaceuticals Corporation; 2020.

MET Inhibitor Trials

- **VISION Study**
  - Open-label, phase 2 study (N = 152)
  - Tepotinib 500 mg by mouth daily in patients with advanced or metastatic NSCLC + METex14 skipping mutation
  - Primary endpoint: objective response rate
    - 46% in combined biopsy group with 11.1 months median duration
    - 49% of 66 patients in liquid-biopsy group
    - 50% of 60 patients in tissue-biopsy group
  - Most common adverse events were peripheral edema (63%) and nausea (26%)

Paik PK, et al. *N Engl J Med*. 2020;383:931-943.

MET Inhibitor Trials

- **GEOMETRY Study**
  - Multiple-cohort, phase 2 study (N = 364)
  - Capmatinib 400 mg by mouth twice daily in patients with advanced or metastatic NSCLC + METex14 skipping mutation or MET amplification gene
  - Primary endpoint: overall response (complete or partial)
    - 41% of 69 patients w/ 1 – 2 previous lines of therapy
    - 68% of 28 patients with no previous treatment
  - Most common adverse events were peripheral edema (51%) and nausea (45%)

Wolf J, et al. *N Engl J Med.* 2020;383:944-57.

Tepotinib Pearls

Administration
- Tepotinib 450 mg by mouth once daily
- Available as 225 mg tablets = 2 tablets required daily
- Administer with food

Monitoring Parameters
- LFTs at baseline, then every 2 weeks during first 3 months, then once a month or as clinically indicated
- AEs: peripheral edema, nausea, hepatotoxicity, pulmonary toxicity
- Adherence

Drug Interactions
- CYP3A4: major substrate
- P-gp: major substrate & inhibitor

LFTs = liver function tests; AEs = adverse events; P-gp = P-glycoprotein

Socinski MA, et al. *J CO Precision Oncology.* 2021;5:653-663.
Tepmetko (tepotinib) [prescribing information]. Rockland, MA: EMD Serono, Inc.; 2021.

Capmatinib Pearls

Administration
- Capmatinib 400 mg by mouth twice daily
- Available as 150 mg and 200 mg tablets = requires maximum 4 tablets daily
- Administer ± food

Monitoring Parameters
- LFTs at baseline, then every 2 weeks during first 3 months, then once a month or as clinically indicated
- AEs: peripheral edema, nausea, hepatotoxicity, pulmonary toxicity
- Adherence

Drug Interactions
- CYP3A4: major substrate
- P-gp: major substrate & inhibitor
- CYP1A2: moderate inhibitor
- Proton pump inhibitors may decrease capmatinib concentration

LFTs = liver function tests; AEs = adverse events; P-gp = P-glycoprotein

Socinski MA, et al. *J CO Precision Oncology.* 2021;5:653-663.
Tabrecta (capmatinib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2020.

LS is a 78-year-old male with stage IV NSCLC adenocarcinoma with METex14 mutation. He is also taking clozapine for schizophrenia. Which targeted therapy could you recommend for LS?

A. Osimertinib 80 mg daily
B. Tepotinib 500 mg daily
C. Capmatinib 400 mg twice daily
D. Capmatinib 400 mg once daily

What's in the never-ending pipeline?

- Adagrasib: June 25, 2021 received FDA breakthrough therapy for KRAS G12C mutation
- Rigosertib: RAS-mimetic + nivolumab for KRAS mutation
- Taletrectinib: TRUST-II – phase 2 for ROS1 mutation
- Mobocertinib: EGFR exon 20 insertion
- Poziotinib: EGFR exon 20 insertion + HER2
- Aflutinib: targeting EGFR T790M
- Telaglenastat: glutaminase inhibitor + osimertinib for advanced EGFR mutant NSCLC
- Osimertinib: NeoADAURA – neoadjuvant osimertinib trial
- And the list goes on and on . . .

Majeed U, et al. *J Hematol Oncol.* 2021;14:108

Questions?

Targeted Therapy Updates in NSCLC

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