PHARMACOTHERAPY UPDATES IN THORACIC ONCOLOGY

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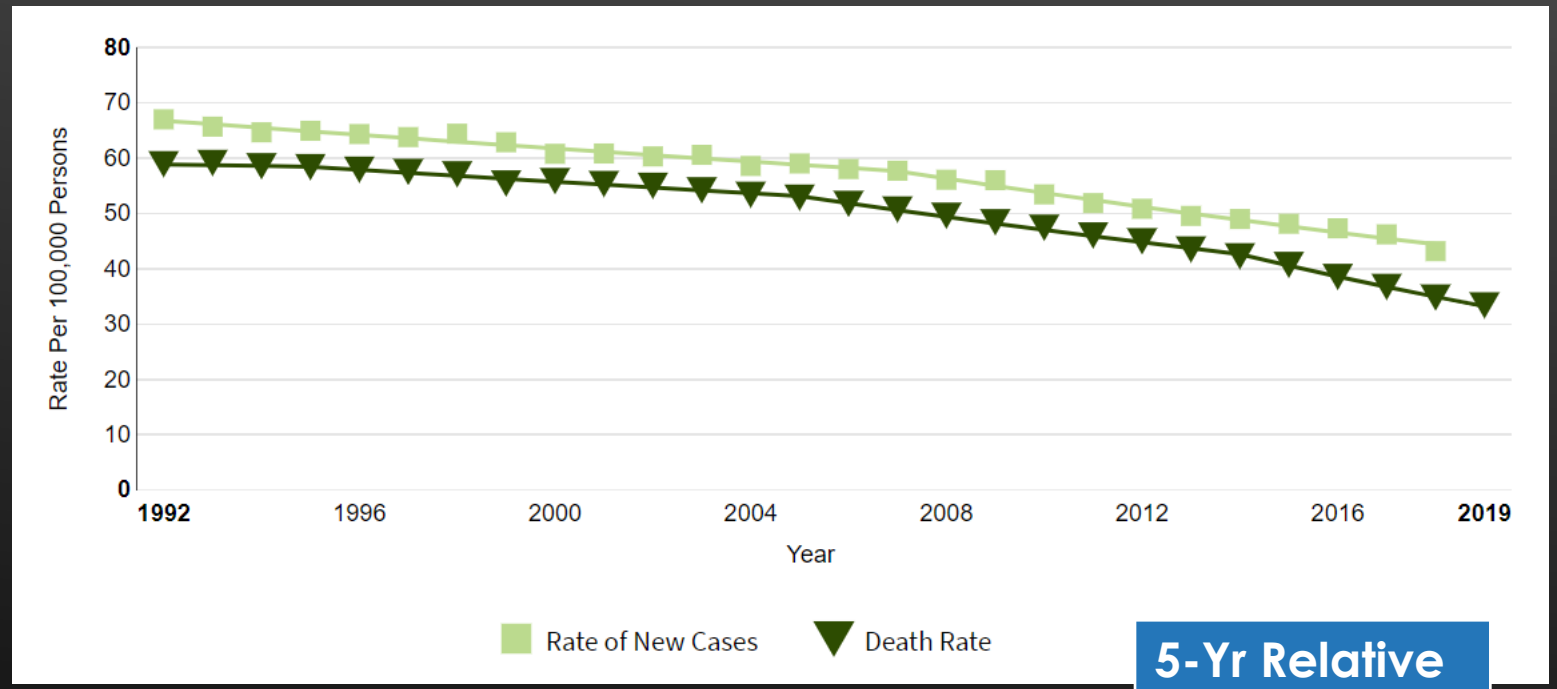
LEARNING OBJECTIVES

- Review emerging biomarkers in the treatment of lung cancer
- Discuss the role of new therapies for the treatment of lung cancer
- Implement individualized therapeutic and monitoring plans based on patient-specific characteristics and toxicities of treatment in the treatment of lung cancer

BACKGROUND

- New Cancer Cases
  - Breast - 284,200
  - Prostate - 248,530
  - Lung - 235,760
  - Colorectal - 149,500

- New Cancer Deaths
  - Lung - 131,880
  - Colorectal - 52,980
  - Pancreas - 48,220
  - Breast - 44,130



5-Yr Relative Survival
21.7%

Image available at: https://seer.cancer.gov/statfacts/html/lungb.html.
Accessed September 27, 2021

PATHOPHYSIOLOGY

- Non-small cell lung cancer – 85%
  - Non-squamous
    - Adenocarcinoma
    - Large Cell
  - Squamous Cell
- Small cell lung cancer – 10%

Genetic Abnormalities	Incidences
KRAS	25 – 30%
EGFR	10 – 15%
ALK	5 – 8%
MET	1 – 6%
RET	1 – 2%
ROS1	1 – 2%
BRAF	1 – 2%
NTRK	0.2%

NON-SMALL CELL LUNG CANCER

KRAS-SOTORASIB

- KRAS protein = "control switch"
  - "Active" – GTP vs "Inactive" GDP
- Diverse group of mutations KRAS
  - KRAS G12C – most common ~ 13%
- KRAS G12C result in "Active" state
  - Higher levels GTP
  - Activation of downstream pathways
  - Uncontrolled cell growth
- Sotorasib
  - Binds only to GDP KRAS G12C
  - Keeps KRAS G12C in inactive state
- Dose 960 mg PO daily
  - Available 120 mg
- Conjugation, CYP3A
- Acid-Reducing Agents
  - Sotorasib 4 hours before or 10 hours after local antacid

FDA approved metastatic NSCLC with KRAS G12C failed one prior systemic therapy

SOTORASIB

- Open label, phase II, N = 124
  - Prior platinum-based chemo
  - PD-1 or PD-L1 inhibitor
  - Combination
- ORR: 37.1% with CR = 3.2%
  - Median time response: 1.4 months
  - Response at 9-months: 57.3%
- mPFS: 6.8 months (95% CI, 5.1 – 8.2)
- mOS: 12.5 months (95% CI, 10.0 – NE)

Adverse Effects	Any Grade	Grade 3 or 4
Diarrhea	42%	5%
Increase AST	39%	9%
Increase ALT	38%	11%
Fatigue	26%	2%
Nausea	26%	1%
Adverse Effects Lead to Dose Modification		34%
Adverse Effects Lead to Dose Discontinuation		9%

NE = could not be estimated

EGFR – EXON 20 INSERTION

- Mutations EGFR major oncogenic driver
  - Exon 19 deletion
  - Exon 21 L858R
  - Exon 20 insertion mutation ~ 12%
- Exon 20 insertion mutation
  - Resistant to EGFR-TKI

- Amivantamab
  - Bispecific EGFR-MET antibody
  - Antibody-dependent cytotoxicity
- Mobocertinib
  - EGFR TKI
  - Inhibits HER2
- Both FDA approved: Exon 20 insertion mutation after failure of platinum-based therapy

EGFR – EXON 20 INSERTION

Drug	Trial	Outcomes (95% CI,)	Adverse Effects (AE): Overall (Grade 3/4)
Amivantamab 1050 mg or 1400 mg IVPB	• Open label, phase I/II • N = 81 • Failed platinum-based tx • Median prior txs: 2	• ORR: 40% with CR = 3 patients • mDOR: 11.1 months (6.9 – NR) • mOS: 22.8 months (14.6 – NR)	• IRR: 65% (2%) • Rash: 78% (3%) • Paronychia: 40% (1%) • Peripheral Edema: 19% (1%) • Diarrhea: 11% (2%) • Due to AE: 13% modify; 4% D/C
Mobocertinib 160 mg PO without regard to food	• Open label, phase I/II • N = 114 • Failed platinum-based tx • Median prior txs: 2	• ORR: 28% • mDOR: 17.5 months (7.4 – 20.3)	• Diarrhea: 92% (22%) • Rash: 78% (1.8%)* • Stomatitis: 46% (4.4%)* • Paronychia: 39% (0.9%)* • Nausea: 37% (4.4%)* • Due to AE: 51% modify; 17% D/C

DOR = Duration of response
IRR = Infusion-related reaction
* = Grade 3 only (no Grade 4 occurred)
NR = Not reached

EGFR – EXON 20 INSERTION

Amivantamab

- Weekly x 4 weeks, then Q14 days
  - Week1: split dose over 2 days
- IRR: Day 1 – 93%, Day 2 – 4%
  - Subsequent infusions – 0.09%

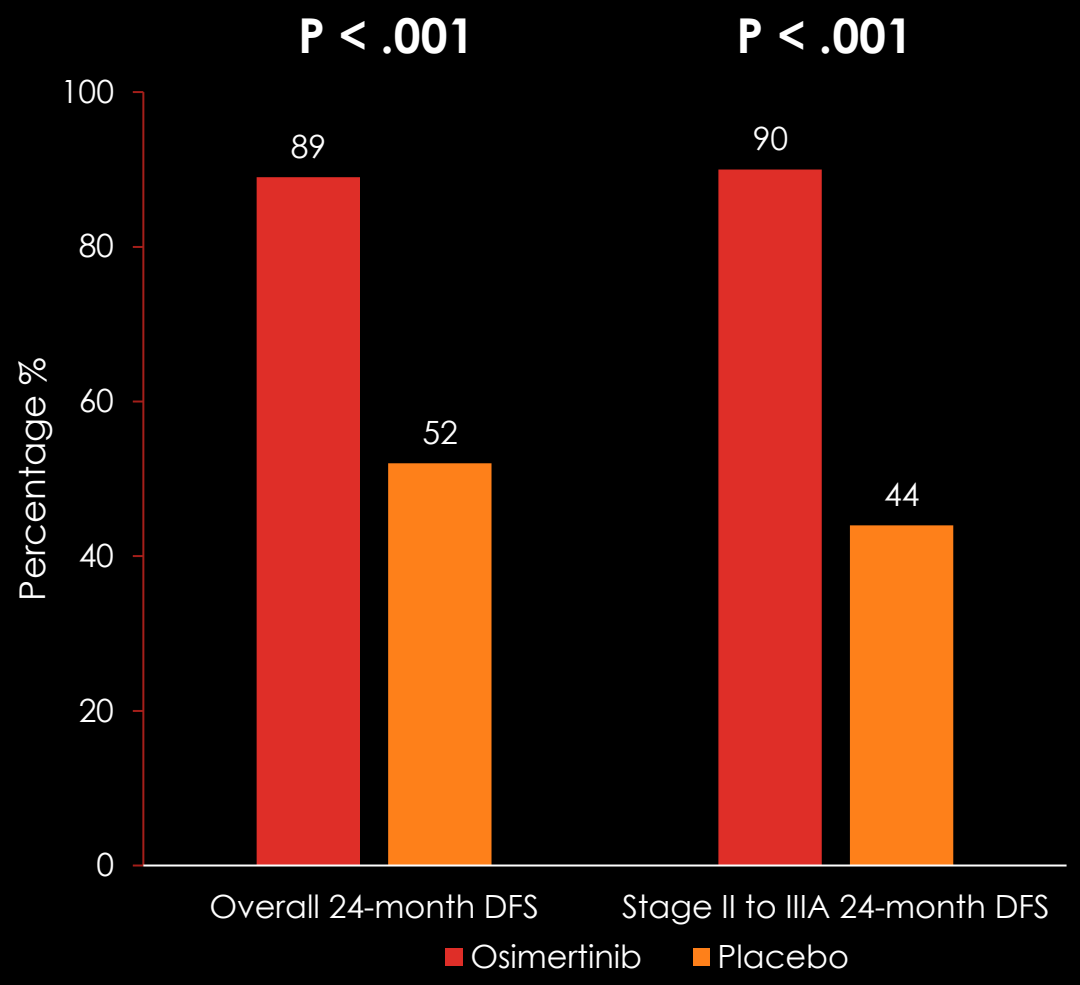
Premedications	
Diphenhydramine 25 – 50 mg or equivalent	With all doses
Acetaminophen 650 – 1000 mg	With all doses
Dexamethasone 10 mg or Methylprednisolone 40 mg or equivalent	Required week 1; optional for subsequent doses

Mobocertinib

- Diarrhea
  - Median time onset: 5 days
  - Median time resolution: 3 days
- QT prolongation
  - 10% overall; 3.5% Grade $\geq$ 3
  - EKG at baseline and periodically
- Heart failure: 2.7% with 1 death
  - LVEF at baseline and during tx

EGFR - ADJUVANT

- Phase III study, ADAURA, N = 682
- Resected, Stages IB – IIIA, EGFR+
- 1:1 Osimertinib or Placebo
- Daily up to 3 years with or without chemotherapy
- DFS benefit regardless:
  - Stage
  - EGFR mutation
  - Chemotherapy or not
- FDA approved – adjuvant treatment of early stage NSCLC for up to 3 years



TARGETED THERAPY - MET

- Tyrosine kinase responsible cell survival
- Alterations in MET drive tumor growth
  - Exon 14 skipping mutation ~ 3 – 4%
  - Amplification ~ 1 – 6%
  - Overexpression
- Associated with poor prognosis

- Capmatinib
  - 400 mg PO BID w/o regard to food
  - 150 and 200 mg tabs
  - CYP3A4
- Tepotinib
  - 450 mg PO daily with food
  - 225 tabs
  - CYP3A4 & 2C8
- Both FDA approved – Metastatic NSCLC with MET exon 14 skipping mutation

TARGETED THERAPY - MET

Drug	Trial	Outcomes (95% CI,)	Adverse Effects (AE): Overall (Grade 3/4)
Capmatinib	• Open label, multi-cohort, phase II • N = 97 • Prior tx, n = 69 • Tx naïve, n = 28	Prior tx: • ORR: 41% • mPFS: 5.4 months (4.2 – 7) Tx naïve: • ORR: 68% with CR: 1 patient • mPFS: 12.4 months (8.2 – NE) CNS ORR: 54% & CR: 4 patients (n = 13)	• Peripheral Edema: 52% (9%) • Nausea: 44% (2.7%) • Fatigue: 32% (8%) • Vomiting: 28% (2.4%) • ↓ Albumin: 68% (1.8%) • Due to AE: 54% modify; 16% D/C
Tepotinib	• Open label, phase II • N = 99 • Prior tx, n = 56 • Tx naïve, n = 43	• ORR: 46% • mPFS: 8.5 months (5.1 – 11) • CNS ORR: 55% (23 – 83)	• Peripheral Edema: 70% (9%) • Nausea: 27% (0.8%) • Fatigue: 27% (1.6%) • Diarrhea: 26% (0.4%) • ↓ Albumin: 76% (9%) • Due to AE: 44% modify; 20% D/C

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NE = Could not be estimated

TARGETED THERAPY - RET

- Tyrosine kinase responsible cell survival
- RET rearrangements result in fusions to other proteins resulting in abnormal signaling
- High risk for brain metastases

Acid-Reducing Agent	Selpercatinib
Proton-pump inhibitor	Take with food
H_2 antagonist	2 hours before or 10 hours after taking H_2 antagonist
Local control antacid	2 hours before or 10 hours after taking antacid

- Selpercatinib
  - RET, VEGFR1, VEGFR3
  - 120 or 160 mg (wt ≥ 50kg) PO BID
  - 40 and 80 mg caps
  - CYP3A4
- Pralsetinib
  - RET, VEGFR2
  - 400 mg PO daily on empty stomach
  - 100 caps
  - CYP3A4, 2D6, 1A2
- Both FDA approved – Metastatic NSCLC with RET fusion positive

TARGETED THERAPY - RET

Drug	Trial	Outcomes (95% CI,)	Adverse Effects (AE): Overall (Grade 3/4)
Selpercatinib	• Open label, phase I/II • N = 144 • Prior tx, n = 105 • Tx naïve, n = 39	Prior tx: • ORR: 64% with CR: 2 patients • mPFS: 16.5 months (13.7 – NE) Tx naïve: • ORR: 85% CNS ORR: 91% & CR: 3 patients (n = 11)	• ↑ AST: 51% (8%) • ↑ ALT: 45% (9%) • Diarrhea: 37% (3.4%) • HTN: 35% (18%) • QT prolongation: 17% (4%) • Due to AE: 42% modify; 5% D/C
Pralsetinib	• Open label, phase I/II • N = 121 • Prior tx, n = 92 • Tx naïve, n = 29	Prior tx: • ORR: 61% with CR: 6% • mPFS: 17.1 months (8.3 – 22.1) Tx naïve: • ORR: 70% with CR: 11% CNS ORR: 56% & CR: 3 patients (n = 9)	• ↑ AST: 74% (2.3%) • ↑ ALT: 49% (2.3%) • Fatigue: 35% (2.3%) • HTN: 28% (14%) • Diarrhea: 24% (3.2%) • Due to AE: 60% modify; 15% D/C

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SMALL CELL LUNG CANCER

RELAPSED/REFRACTORY SCLC

- Difficult to treat
- Response = time of relapse
  - ORR: 20 – 30% (≥ 90 days)
  - ORR: < 10% (< 90 days)
- Variety of treatment options

- Lurbinectedin
  - Binds to guanine residues in minor groove of DNA
  - Forms adducts
  - Bending of DNA helix towards major groove
- 3.2 mg/m2 IVPB every 21 days
- CYP3A4
- FDA approved metastatic SCLC failed platinum-based chemotherapy

LURBINECTEDIN

- Open label, phase II, N = 105
  - Prior platinum-based chemo
  - Immunotherapy ~ 8%
- ORR: 35.2% (95% CI, 26.2 – 45.2)
  - ≥ 90 days ORR: 45%
  - < 90 days ORR: 22.2%
- mOS: 9.3 months (95% CI, 6.3 – 11.8)
  - ≥ 90 days mOS: 11.9 months
  - < 90 days mOS: 5.0 months

Adverse Effects	Any Grade	Grade 3 or 4
Fatigue	77%	12%
↓ Hgb	74%	10%
↑ ALT	66%	4%
↓ Plts	37%	7%
↑ AST	26%	2%
Adverse Effects Lead to Dose Modification		30.5%
Adverse Effects Lead to Dose Discontinuation		1.9%

SUPPORTIVE CARE - TRILACICLIB

- Stem cells dependent on cyclin-dependent kinase (CDK) 4/6
- Trilaciclib arrests stem cells in G1 phase
- "Myeloprotective" effect from chemotherapy
- 240 mg/m_2 IVPB over 30 minutes
- Must complete within 4 hrs of chemo for each day chemo
- Inhibitor of OCT2, MATE1, MATE-2K
- Drug Interactions
  - Cisplatin
  - Metformin
- FDA approved decrease incidence of chemotherapy-induced myelosuppression when giving platinum/etoposide or topotecan containing regimens in extensive stage SCLC

SUPPORTIVE CARE - TRILACICLIB

	% Patients with severe neutropenia	
Study	Trilaciclib	Placebo
Study 1: Tx naïve, EPA, n = 105	1.9%	49.1%
Study 2: Tx naïve, EP, n = 77	5.1%	42.1%
Study 3: Prior tx, topotecan, n = 61	40.6%	75.9%

E = Etoposide
P = Carboplatin
A = Atezolizumab

Adverse Effects	Any Grade	Grade 3 or 4
Fatigue	34%	3%
↓ Calcium	24%	< 1%
↓ Potassium	22%	6%
↓ Phosphorus	21%	7%
IRR	8%	0%
Adverse Effects Lead to Dose Modification		4.1%
Adverse Effects Lead to Dose Discontinuation		9%

REMOVAL OF FDA APPROVAL

- 2018 – Nivolumab accelerated approval for SCLC who failed platinum-based chemotherapy and at least 1 other line of therapy
- CheckMate-451 and CheckMate-331 failed to meet OS endpoints
- Jan 2021 – BMS withdraws indication for Nivolumab for SCLC
- Still an option NCCN Guidelines SCLC version 1.2022

SUMMARY

- New biomarker targets in fight against lung cancer
  - KRAS
  - Exon 20 Insertion mutation
  - MET
  - RET
- New drugs in our arsenal
- New ways to treat lung cancer

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