

IASLC



2023 Targeted Therapies of Lung Cancer Meeting


FEBRUARY 22-25, 2023
SANTA MONICA, CALIFORNIA

TTLC 2023 PROGRAM BOOK

#TTLC23



CONQUERING THORACIC CANCERS WORLDWIDE



Submit Your 2023 Cancer Care Team Award Nominations

NOMINATIONS WILL BE ACCEPTED MARCH 15-APRIL 26, 2023

The IASLC Cancer Care Team Award honors multidisciplinary teams, as nominated by the patients they serve. Exceptional care teams offer the patient seamless and informed communication, as well as an individualized treatment plan based on not just the patient's needs, but the patient's wishes. The Cancer Care Team Award aims to highlight this kind of worldwide, outstanding care.

**Nominate your care team
today at
<https://bit.ly/2023ccta>**



INTERNATIONAL
ASSOCIATION
FOR THE STUDY
OF LUNG CANCER

The IASLC Cancer Care Team Award was established in memory of Marilyn Holman, who passed away from lung cancer in 2016. By recognizing Cancer Care Teams across the globe, we hope to spread awareness and speak to the outstanding care that is possible for all lung cancer patients, from the time of diagnosis through treatment.

We invite and encourage individual patients with lung cancer and/or their caregivers to nominate a multidisciplinary care team who they feel provided exceptional care. Only IASLC Members are eligible to submit nominations for the Cancer Care Team Award. If you are not yet a member, visit www.iaslc.org/membership for information on how to join. IASLC Membership is complimentary for patients and their family members and caregivers. The deadline to submit nominations is April 26, 2023. An international panel will choose one winning team from each of the four regions – North America, Latin America, Europe, and Asia/ROW. Winning teams will be announced during the 2023 World Conference on Lung Cancer in Singapore.

2022 IASLC Care Team Award Recipients



North American Recipient: Baptist Cancer Center, Memphis, Tennessee



Latin American Recipient: Instituto Nacional del Tórax, Providencia, Chile



Asia/ROW Recipient: Shanghai Pulmonary Hospital, Affiliated to Tongji University, Shanghai, China



2023 World Conference on Lung Cancer

SEPTEMBER 9-12, 2023 | SINGAPORE

Abstract Submission Is Open!

Showcase your research and contribute to discussions that will shape the future of treatments in lung cancer and thoracic malignancies at the 2023 World Conference on Lung Cancer.

Deadline to submit: April 14, 2023.

CONNECT WITH US



#WCLC23

wclc2023.iaslc.org/call-for-abstracts

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MEETING SECRETARIAT

International Conference Services Ltd. (ICS)

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www.icsevents.com



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WELCOME MESSAGE

01 | WELCOME MESSAGE

On behalf of the International Association for the Study of Lung Cancer (IASLC), we are pleased to welcome you to the Targeted Therapies of Lung Cancer Meeting (TTLC2023) at the Fairmont Miramar in Santa Monica, California, United States. After two years of virtual meetings, we are thrilled to see you again in person. We are pleased to offer virtual participation and livestreaming of all sessions allowing anyone from anywhere to join this unique meeting.

The IASLC Targeted Therapies of Lung Cancer Meeting is a dynamic meeting with a long tradition. Meeting presenters will summarize the data on relevant targets for new therapies and share data on preclinical and early clinical data for each of the drugs directed against these targets.

We would like to extend our gratitude and thanks to all industry supporters for their support of the IASLC Targeted Therapies of Lung Cancer Meeting and the IASLC. Without them this meeting would not have been possible.

Thank you for joining us in Santa Monica, California.

We look forward to hosting all of you over the next three days.

Best Regards,



Paul A. Bunn, Jr.
MD

TTLC 2023 Meeting Chair



Charu Aggarwal
MD

TTLC 2023 Meeting Chair



Lecia Sequist
MD

TTLC 2023 Meeting Chair



Joel Neal
MD, PhD

TTLC 2023 Meeting Chair



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IASLC

02 | IASLC

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

The International Association for the Study of Lung Cancer (IASLC) is the only global organization dedicated to the study of lung cancer. Since its founding in 1974, the association's membership has grown to more than 8,000 lung cancer specialists from all disciplines and more than 100 countries.

By hosting global conferences, funding cutting-edge research, and educating the health care community and the public about thoracic cancers, the IASLC works to alleviate the burden lung cancer places on patients, families, and communities.

The IASLC mission is:

- ➔ To embrace the study of the etiology, epidemiology, prevention, diagnosis, treatment and all other aspects of lung cancer and other thoracic malignancies.
- ➔ To provide education and information about lung cancer and other thoracic malignancies to IASLC members, to the medical community at large, and to the public
- ➔ To use all available means to eliminate lung cancer and other thoracic malignancies as a health threat for the individual patient and throughout the world.

IASLC



**International Association for the
Study of Lung Cancer**

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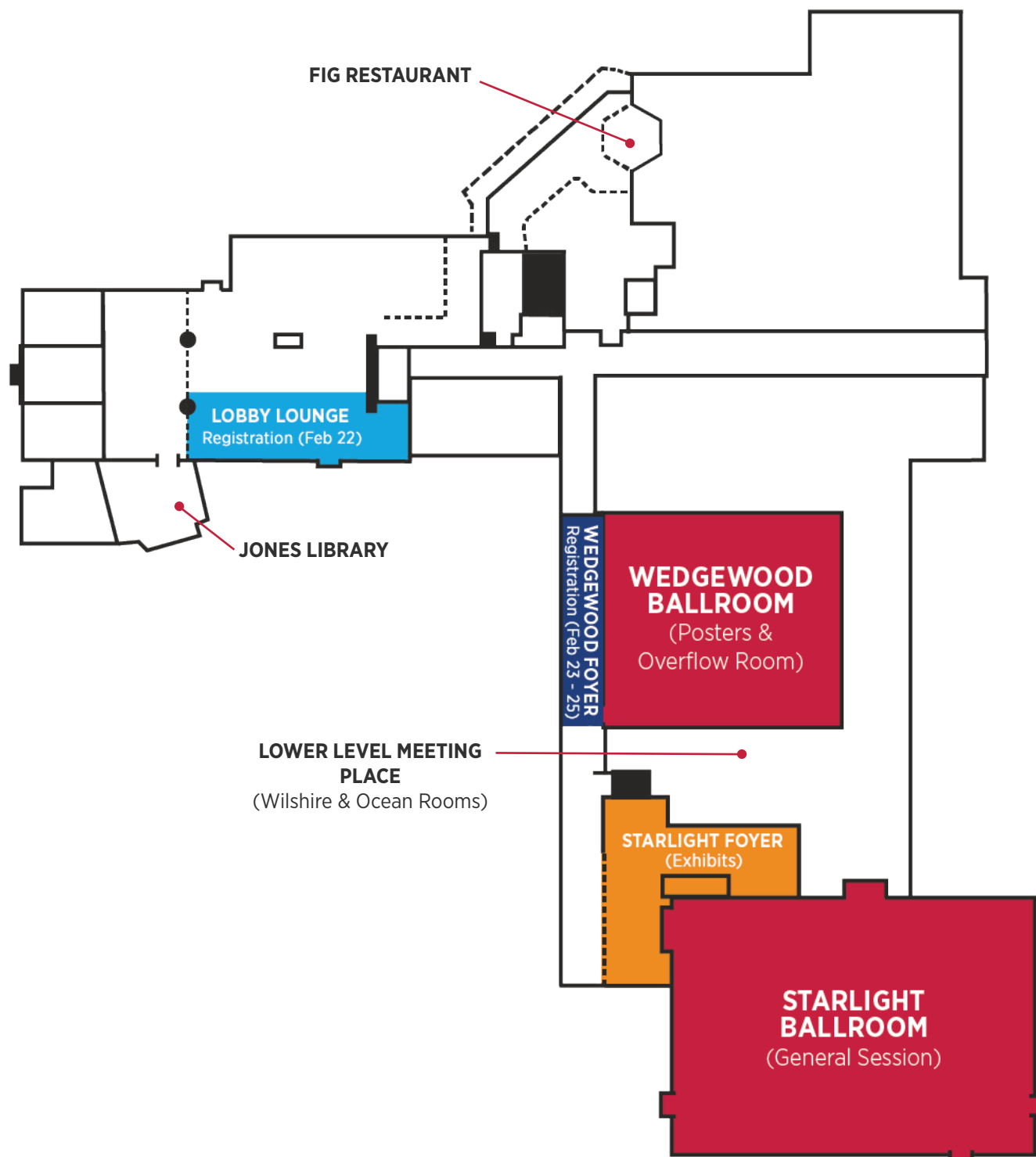


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VENUE FLOORPLAN

03 | VENUE FLOORPLAN

FAIRMONT MIRAMAR - HOTEL LEVEL





4

PROGRAM

04 | PROGRAM

WEDNESDAY, FEBRUARY 22



Registration Desk Opening Hours: **15:00 – 20:30**



Hotel Lobby Lounge

15:15 - 15:45

Registration and Catered Menu

15:45 - 16:45

CME/MOC Credit - Facilitating Progress in the Treatment of SCLC: How to Optimize the Use of Current Systemic Options and Accelerate the Clinical Transition of Investigational Approaches

This activity is supported by independent educational grants from AstraZeneca and Jazz Pharmaceuticals, Inc.

Starlight Ballroom

FOOD PROVIDED

LIVE-STREAMED SESSION

17:30 - 18:30

Opening Reception

Starlight Foyer

REFRESHMENTS PROVIDED



Jazz Pharmaceuticals



18:30 - 20:00

Opening Dinner with Keynote Speaker

Starlight Ballroom

DINNER PROVIDED

LIVE-STREAMED SESSION

Chairs: Paul A. Bunn, Jr., University of Colorado Cancer Center, United States
Lecia Sequist, Massachusetts General Hospital, United States

19:20

OK01 - Progress and Promise in Small Cell Lung Cancer

Lauren Byers, MD Anderson Cancer Center, United States

19:50

Q&A

WEDNESDAY, FEBRUARY 22, 2023

04 | PROGRAM

THURSDAY, FEBRUARY 23



Registration Desk Opening Hours: **06:30 – 18:00**



Wedgewood Foyer



06:30 – 08:00 Networking Breakfast

Wedgewood Ballroom



**BREAKFAST
WILL BE PROVIDED**

07:00 – 08:00

Optimizing Testing Strategies: How to Leverage Liquid Biopsy Into the Diagnostic Algorithm for Metastatic NSCLC by AstraZeneca

Starlight Ballroom

FOOD PROVIDED

Chair: Charu Aggarwal, University of Pennsylvania, United States

Presenters: Brendon Stiles, Montefiore Medical System, Albert Einstein College of Medicine, United States, Jeff Thompson, University of Pennsylvania, United States

07:00 – 07:50

Panel Discussion

07:50 – 08:00

Q&A

08:15 – 10:05

Session 1: Targeted Therapies - EGFR, HER2 and MET

Starlight Ballroom

LIVE-STREAMED SESSION

Chairs: Yasir Elamin, MD Anderson Cancer Center, United States
Karen Reckamp, Cedars-Sinai, United States

08:15

S1.01 - First-Line Therapy for Classic EGFR Mutations: What's Next?

Christine Lovly, Vanderbilt University Medical Center, United States

08:25

S1.02 - Rare EGFR Mutations (Non Exon 20): Do We Know Enough to Treat These Tumors Differently?

Xiuning Le, MD Anderson Cancer Center, United States

08:35

S1.03 - EGFR Acquired Resistance: C797 and Bypass Pathways

Julia Rotow, Dana-Farber Cancer Institute, United States

08:45

S1.04 - Histologic Transformation as an EGFR Resistance Mechanism

Helena Yu, MSKCC, United States

08:55

S1.05 - EGFR Exon 20 and HER2

Zofia Piotrowska, Massachusetts General Hospital, United States

09:05

S1.06 - MET Exon 14

Joshua Sabari, NYU Langone Health Perlmutter Cancer Center, United States

09:15

S1.07 - Checkpoint Inhibition for Driver Mutations - Is There a Way Forward?

Joshua Reuss, Georgetown Lombardi Cancer Center, United States

09:25

Panel Discussion:

Elaine Shum, NYU Perlmutter Cancer Center, United States

Hatim Husain, University of California San Diego, United States

Erin Schenk, University of Colorado, Anschutz Medical Center, United States

Frederick Wilson, Yale University, United States

Ryan Gentzler, University of Virginia, United States

Pasi Janne, Dana-Farber Cancer Institute, United States

THURSDAY, FEBRUARY 23, 2023

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THURSDAY, FEBRUARY 23

THURSDAY, FEBRUARY 23, 2023

09:55

Session 1: Debate

S1D.01 - After Progression on TKI, Chemo + Continued TKI Should Be Standard - Yes

Balazs Halmos, Montefiore, United States

S1D.02 - After Progression on TKI, Chemo + Continued TKI Should Be Standard - No

Mark Socinski, AdventHealth Cancer Institute, United States

10:05 - 10:20

Patient Advocate Talk

▶ LIVE-STREAMED SESSION

PA01 - The Patient Voice in Clinical Trial Design

Jill Feldman, EGFR Resisters, United States



10:20 - 10:45 Networking Break

Starlight Foyer



REFRESHMENTS
WILL BE PROVIDED

10:45 - 12:25

Session 2: Targeted Therapies - ALK, ROS, RET, NTRK, NRG1

Starlight Ballroom

▶ LIVE-STREAMED SESSION

Chairs: Jaime Schneider, Massachusetts General Hospital, United States

Sai-Hong Ou, University of California Irvine, United States

10:45

S2.01 - Current Approaches to 1st Line ALK and ROS

Tejas Patil, University of Colorado, United States

10:55

S2.02 - ALK Resistance

Angel Qin, University of Michigan Rogel Cancer Center, United States

11:05

S2.03 - ROS1 Resistance

Jessica Lin, Massachusetts General Hospital, United States

11:15

S2.04 - RET

Alexander Drilon, MSKCC, United States

11:25

S2.05 - NTRK and NRG1

Jyoti Patel, Northwestern University, United States

11:35

S2.06 - Could We Use Vaccines Against ALK and Other Targets?

Mark Awad, Dana-Farber Cancer Institute, United States

11:45

Panel Discussion:

Kathryn Mileham, Levine Cancer Institute, United States

Catherine Shu, Columbia University Medical Center, United States

Gregory Riely, Memorial Sloan Kettering Cancer Center, United States

David Stewart, University of Ottawa, Canada

Amy Cummings, David Geffen School of Medicine At UCLA, United States

Ana Velazquez Manana, University of California San Francisco, United States

12:15

Session 2: Debate

S2D.01 - Lorlatinib Should Be Given to All ALK Patient 1st Line Treatment - Yes

Lyudmila Bazhenova, University of California San Diego, United States

S2D.02 - Lorlatinib Should Be Given to All ALK Patient 1st Line Treatment - No

Justin Gainor, Massachusetts General Hospital, United States

04 | PROGRAM

THURSDAY, FEBRUARY 23



12:25 – 13:30 **Networking Lunch**
Driveway under FIG Tree & Wedgewood Ballroom



**LUNCH WILL
BE PROVIDED**

AstraZeneca 

13:30 – 15:20

Session 3: SCLC
Starlight Ballroom

 **LIVE-STREAMED SESSION**

Chairs: Catherine Meador, Massachusetts General Hospital, United States
Shadia Jalal, Indiana University, United States

- 13:30** **S3.01 - Recent Advances and Unanswered Questions in SCLC Biology**
Taofeek Owonikoko, UPMC Hillman Cancer Center, United States
- 13:40** **S3.02 - Immunotherapy Drugs in SCLC**
Ticiana Leal, Emory University, United States
- 13:50** **S3.03 - ADCs in SCLC**
Anne Chiang, Yale University, United States
- 14:00** **S3.04 - Other Novel Drugs in SCLC**
Christine Hann, Johns Hopkins University School of Medicine, United States
- 14:10** **S3.05 - Novel Biomarkers in SCLC**
Wade Iams, Vanderbilt University Medical Center, United States
- 14:20** **S3.06 - Cellular Therapy in SCLC**
Carl Gay, University of Texas MD Anderson Cancer Center, United States
- 14:30** **S3.07 - Consolidation Strategies (Both IO and Radiation)**
Nagla Abdel Karim, Inova Schar Cancer Institute, United States
- 14:40** **Panel Discussion:**
Triparna Sen, Icahn School of Medicine at Mount Sinai, United States
Jacob Sands, Dana-Farber Cancer Institute, United States
Jennifer Carlisle, Emory University, United States
Yu Shyr, Vanderbilt University Medical Center, United States
So Yeon Kim, Yale Cancer Center, United States
Misty Shields, Indiana University School of Medicine, United States
- 15:10** **Session 3: Debate**

S3D.01 - Consolidation Chest Radiation Should Be Given in ES-SCLC - Yes
Charles Simone, New York Proton Center and Memorial Sloan Kettering Cancer Center, United States

S3D.02 - Consolidation Chest Radiation Should Be Given in ES-SCLC - No
Lawrence Einhorn, Indiana University, United States



15:20 – 15:45 **Networking Break**
Starlight Foyer



**REFRESHMENTS
WILL BE PROVIDED**

MIRATI
THERAPEUTICS

THURSDAY, FEBRUARY 23, 2023

04 | PROGRAM

THURSDAY, FEBRUARY 23



THURSDAY, FEBRUARY 23, 2023

15:45 - 17:25

Session 4: Targeted Therapies - KRAS, BRAF, New Targets

Starlight Ballroom

LIVE-STREAMED SESSION

Chairs: Kristen Marrone, Johns Hopkins University School of Medicine, United States
Mark Kris, MSKCC, United States

- 15:45 **S4.01 - G12C Inhibitors + Immunotherapy**
Rebecca Heist, MGH, United States
- 15:55 **S4.02 - G12C Inhibitors + Other Combinations**
Alexander Spira, Virginia Cancer Specialists/US Oncology Research, United States
- 16:05 **S4.03 - Pan RAF Inhibitor Trials**
Shirish Gadgeel, Henry Ford Cancer Institute/Henry Ford Health, United States
- 16:15 **S4.04 - SHP2 Inhibitor Trials**
Kathryn Arbour, Memorial Sloan Kettering Cancer Center, United States
- 16:20 **S4.05 - Trials in KRAS Mutants with Co Mutations**
Ferdinand Skoulidis, The University of Texas MD Anderson Cancer Center, United States
- 16:30 **S4.06 - SOS1 Inhibitor Trials**
Bob Li, Memorial Sloan Kettering Cancer Center, United States
- 16:35 **S4.07 - Resistance Trials with KRAS or BRAF Mutants**
Ibiayi Dagogo-Jack, Massachusetts General Hospital, United States
- 16:45 **S4.08 - Overview of the Lung MAP Trial**
Roy Herbst, Yale Cancer Center, United States
- 16:50 **Panel Discussion:**
Rajwanth Veluswamy, Icahn School of Medicine at Mount Sinai, United States
Collin Blakely, University of California San Francisco, United States
Daniel Morgensztern, Washington University, United States
Grace Dy, Roswell Park Cancer Institute, United States
David Gerber, University of Texas Southwestern Medical Center, United States
Nathaniel Myall, Stanford Cancer Institute, United States
- 17:15 **Session 4: Debate**
 - S4D.01 - Patients Should Receive Targeted Therapy First for BRAF/MET - Yes**
Scott Gettinger, Yale Cancer Center, United States
 - S4D.02 - Patients Should Receive Targeted Therapy First for BRAF/MET - No**
Julie Brahmer, Johns Hopkins Kimmel Cancer Center, United States

17:25 - 18:25

Poster Viewing Reception with Poster Presenters in Attendance

Wedgewood Ballroom

REFRESHMENTS PROVIDED



04 | PROGRAM

THURSDAY, FEBRUARY 23

18:45 - 21:00

Early Career Session for Fellows

Wedgewood Ballroom



Chairs: John Minna, University of Texas Southwestern Medical Center, United States
Susan Scott, Johns Hopkins University, United States

- 18:45** **Dinner and Networking**
- 19:15** **EC01 - Leading a Lab and Seeing Patients: Finding the Right Balance**
John Heymach, MD Anderson Cancer Center, United States
- 19:20** **EC02 - How to Succeed as a Clinical Trialist**
Paul Paik, Memorial Sloan Kettering Cancer Center, United States
- 19:25** **EC03 - A Career at the FDA**
Harpreet Singh, FDA, United States
- 19:30** **EC04 - Partnering with Patients for Real World Data Collection and PROs**
Janet Freeman-Daily, The ROS1ders, United States
- 19:35** **EC05 - How Could Social Media Improve My Career Trajectory**
Stephen Liu, Georgetown University, United States
- 19:40** **EC06 - Transition to Industry**
Maria Catherine Pietanza, Merck & Co, United States
- 19:45** **EC07 - Non University Based Oncology Careers**
David Spigel, Sarah Cannon, United States
- 19:50** **EC08 - Oncology Careers at VA**
Millie Das, Stanford University/VA Palo Alto, United States
- 19:55** **EC09 - Conducting Cooperative Group Clinical Trials**
Thomas Stinchcombe, Duke Cancer Institute, United States
- 20:00** **EC10 - Collaboration Across Specialties**
Dara Aisner, University of Colorado, United States
- 20:05** **EC11 - How to Publish Your Research**
Antoinette Wozniak, University of Pittsburgh, United States
- 20:10** **Discussion with All Speakers**

THURSDAY, FEBRUARY 23, 2023

04 | PROGRAM

THURSDAY, FEBRUARY 23

18:00 – 18:30

Registration and Dinner

18:30 – 19:30

CME/MOC Credit - Refining Precision Decisions in NSCLC With Common and Less Common EGFR Mutations: Navigating Testing and Treatment Throughout the Disease Continuum

This activity is supported by independent educational grants from AstraZeneca, Janssen Biotech, Inc., administered by, Janssen Scientific Affairs, LLC, and Takeda Pharmaceuticals U.S.A., Inc.

Starlight Ballroom

 DINNER PROVIDED

 LIVE-STREAMED SESSION

Chair: Natasha Leighl, Princess Margaret Cancer Centre, Canada

Presenter: Joshua Sabari, NYU Langone Health Perlmutter Cancer Center, United States

Welcome, Introduction, and Goal Setting

Refining Precision Decisions in Biomarker Testing and Targeted Treatment of EGFR-Mutated NSCLC

Optimizing Biomarker Testing and Laying the Foundation for Targeted Treatment of NSCLC With Common and Less Common EGFR Mutations: First, Find the Targets

The Evolving Role of Current and Novel/Emerging EGFR-Targeted Therapies and Combinations in NSCLC: Accelerating Research to Improve Patient Outcomes

Q&A, Reflections, and Conclusions

THURSDAY, FEBRUARY 23, 2023

04 | PROGRAM

FRIDAY, FEBRUARY 24



Registration Desk Opening Hours: **06:30 – 18:00**



Wedgewood Foyer



06:30 – 08:00 Networking Breakfast
Wedgewood Ballroom



**BREAKFAST
WILL BE PROVIDED**

07:00 – 08:00

Women in Thoracic Oncology and Career Development: Sponsorship in Academic Medicine

Wilshire I



BREAKFAST PROVIDED

Chairs: Charu Aggarwal, University of Pennsylvania, United States
Lecia Sequist, Massachusetts General Hospital, United States

Panel Discussion:

Frances Shepherd, Princess Margaret Cancer Centre, Canada

Leora Horn, AstraZeneca, United States

Brendon Stiles, Montefiore Medical System, Albert Einstein College of Medicine, United States

Narjust Florez, Dana-Farber Cancer Institute, United States

Thomas Lynch, Fred Hutch Cancer Center, United States

Karen Kelly, International Association for the Study of Lung Cancer, United States

Bailey Fitzgerald, Icahn School of Medicine at Mount Sinai, United States

Deborah Doroshov, Icahn School of Medicine at Mount Sinai, United States

08:15 – 09:55

Session 5: Locally Advanced NSCLC

Starlight Ballroom



LIVE-STREAMED SESSION

Chairs: Eric Singhi, University of Texas MD Anderson Cancer Center, United States
Helen Ross, Banner MD Anderson Cancer Center, United States

08:15

S5.01 - Innovations in Radiation Therapy

Kristin Higgins, Winship Cancer Institute of Emory University, United States

08:25

S5.02 - Building Upon the Success of Consolidative Immunotherapy

Greg Durm, Indiana University, United States

08:35

S5.03 - Concurrent Chemo+IO Approaches with Radiation

Nathan Pennell, Cleveland Clinic, United States

08:45

S5.04 - Targeted Therapy in Consolidation Setting

Howard (Jack) West, City of Hope Comprehensive Cancer Center, United States

08:55

S5.05 - Immunotherapy in the Setting of SBRT

Steven Lin, MD Anderson Cancer Center, United States

09:05

S5.06 - Oligometastatic vs Oligorecurrent Disease

Puneeth Iyengar, University of Texas Southwestern Medical Center, United States

09:15

Panel Discussion:

Christine Bestvina, University of Chicago Medicine, United States
Chandra Belani, Penn State Cancer Institute, United States
Megan Daly, UC Davis Comprehensive Cancer Center, United States
Diane Tseng, Fred Hutchinson Cancer Center, United States
Young Chae, Northwestern University, United States
Andrea Bezjak, Princess Margaret Cancer Center, Canada

09:45

Session 5: Debate**S5D.01 - Consolidation Immunotherapy Should Be Used in Biomarker Selected Patients - Yes**

David Gandara, UC Davis Comprehensive Cancer Center, United States

S5D.02 - Consolidation Immunotherapy Should Be Used in Biomarker Selected Patients - No

Everett Vokes, University of Chicago, United States



09:55 – 10:30 Networking Break

Starlight Foyer



**REFRESHMENTS
WILL BE PROVIDED**

TEMPUS

10:30 - 11:30

Best Fellows Oral Abstract Session

Starlight Ballroom

LIVE-STREAMED SESSION

Chairs: Paul A. Bunn, Jr., University of Colorado Cancer Center, United States
 Lecia Sequist, Massachusetts General Hospital, United States
 Charu Aggarwal, University of Pennsylvania, United States
 Joel Neal, Stanford, United States

10:30

OA01.01 - Impact of Baseline Clinicopathologic and Genomic Features on Outcomes to KRAS G12C Inhibitors in Patients with NSCLC

Giuseppe Lamberti, Dana-Farber Cancer Institute, United States

10:40

Q&A

10:45

OA01.02 - CNS Metastases in KRAS G12D-Mutant Non-Small Cell Lung Cancer: Frequency and Associated Clinicopathologic Factors

Alissa Cooper, Massachusetts General Hospital, United States

10:55

Q&A

11:00

OA01.03 - First-Line Osimertinib in Patients with Uncommon EGFR-Mutated Non-Small Cell Lung Cancer

Tia Cheunkarndee, Johns Hopkins University School of Medicine, United States

11:10

Q&A

11:15

OA01.04 - Risk of Further Progression or Death Among Durable Progression-Free Survivors with Non-Small Cell Lung Cancer in PD-1 Blockade Trials: Guidance on Imaging Surveillance Interval

Lei Deng, Roswell Park Comprehensive Cancer Center, United States

11:25

Q&A

04 | PROGRAM

FRIDAY, FEBRUARY 24

FRIDAY, FEBRUARY 24, 2023

11:30 - 13:10

Session 6: Mesothelioma/Thymic Carcinoma

Starlight Ballroom

 LIVE-STREAMED SESSION

Chairs: Aaron Mansfield, Mayo Clinic, United States
Penelope Bradbury, Princess Margaret Cancer Centre, Canada

- 11:30 S6.01 - Biomarkers in Thymic Malignancies and Mesothelioma**
Michael Offin, Memorial Sloan Kettering Cancer Center, United States
- 11:40 S6.02 - Immunotherapy in Thymic Malignancies**
Sukhmani Padda, Cedars-Sinai Medical Center, United States
- 11:50 S6.03 - Targeted Therapy in Thymic Malignancies**
Dwight Owen, The Ohio State University, United States
- 12:00 S6.04 - Surgical Considerations for Thymic Malignancies**
Jessica Donington, University of Chicago, Section Thoracic Surgery, United States
- 12:10 S6.05 - Frontline Immunotherapy vs Chemotherapy in Mesothelioma**
Anne Tsao, MD Anderson Cancer Center, United States
- 12:20 S6.06 - Emerging Targeted Therapies in Mesothelioma**
Melina Marmarelis, University of Pennsylvania, United States
- 12:30 Panel Discussion:**
Matthew Gubens, University of California San Francisco, United States
Prasad Adusumilli, Memorial Sloan Kettering Cancer Center, United States
Jeremy Cetnar, Oregon Health & Science University, United States
Kaushal Parikh, Mayo Clinic, United States
Aaron Lisberg, University of California Los Angeles, United States
- 13:00 Session 6: Debate**
- S6D.01 - Newly Diagnosed Patients with Mesothelioma Should Receive Immunotherapy Prior to Surgery - Yes**
Marjorie Zauderer, Memorial Sloan Kettering Cancer Center, United States
- S6D.02 - Newly Diagnosed Patients with Mesothelioma Should Receive Immunotherapy Prior to Surgery - No**
Harvey Pass, NYU Langone Medical Center, United States



13:10 - 14:15 Networking Lunch
Driveway under FIG Tree & Wedgewood Ballroom



**LUNCH WILL
BE PROVIDED**

REGENERON®

04 | PROGRAM

FRIDAY, FEBRUARY 24

FRIDAY, FEBRUARY 24, 2023

14:15 - 15:45

Session 7: Immunotherapy - Cellular Therapies & Biomarkers

Starlight Ballroom

 LIVE-STREAMED SESSION

Chairs: Hirva Mamdani, Karmanos Cancer Institute, United States
Fred Hirsch, Mount Sinai, New York, United States

- 14:15** **S7.01 - Tissue Based Predictors of Immunotherapy**
Natalie Vokes, MD Anderson Cancer Center, United States
- 14:25** **S7.02 - Blood Based Predictors of Immunotherapy**
Valsamo Anagnostou, Johns Hopkins School of Medicine, United States
- 14:35** **S7.03 - Immune Microenvironment as Biomarker for Immunotherapy**
Brian Henick, Columbia University, United States
- 14:45** **S7.04 - Overview of Cell Therapy: TIL & Autologous Therapy**
Benjamin Creelan, H Lee Moffitt Cancer Center, United States
- 14:55** **S7.05 - Transgenic Cellular Therapies - Current and Promising Targets**
Vincent Lam, Johns Hopkins University School of Medicine, Sidney Kimmel Comprehensive Cancer Center, United States
- 15:05** **Panel Discussion:**
Salman Puneekar, NYU Perlmutter Cancer Center, United States
Kim Norris, Lung Cancer Foundation of America, United States
Adam Schoenfeld, MSKCC, United States
Jianjun Zhang, University of Texas MD Anderson Cancer Center, United States
Christian Rolfo, Mount Sinai Health System, United States
Jia Luo, Dana-Farber Cancer Institute, United States
John Wrangle, Medical University of South Carolina, United States
- 15:35** **Session 7: Debate**
- S7D.01 - Patients Treated with Neo-adjuvant Chemo IO Who Do Not Achieve a Path CR Should Be Followed With Observation Only - Yes**
Rosalyn Juergens, McMaster University, Canada
- S7D.02 - Patients Treated with Neo-adjuvant Chemo IO Who Do Not Achieve a Path CR Should Be Followed With Observation Only - No**
Tina Cascone, University of Texas MD Anderson Cancer Center, United States



15:45 - 16:15 **Networking Break**
Starlight Foyer



**REFRESHMENTS
WILL BE PROVIDED**

MIRATI
THERAPEUTICS

04 | PROGRAM

FRIDAY, FEBRUARY 24

FRIDAY, FEBRUARY 24, 2023

16:15 – 18:05

Session 8: Immunotherapy for Advanced NSCLC - Checkpoint Inhibitors

Starlight Ballroom

▶ LIVE-STREAMED SESSION

Chairs: Regan Memmott, The Ohio State University, James Comprehensive Cancer Center, United States, Vamsidhar Velcheti, New York University, United States

- 16:15 S8.01 - IO Agents in Clinical Practice**
Natasha Leigh, Princess Margaret Cancer Centre, Canada
- 16:25 S8.02 - Immune Pathway Antagonists**
Rachel Sanborn, Earle A. Chiles Research Institute Providence Portland, United States
- 16:35 S8.03 - Immune Pathway Agonists**
Edward Garon, David Geffen School of Medicine at UCLA, United States
- 16:45 S8.04 - Combination IO and Anti-angiogenesis**
Deborah Doroshow, Icahn School of Medicine at Mount Sinai, United States
- 16:55 S8.05 - Combination IO and Targeted Therapy**
Adrian Sacher, Princess Margaret Cancer Centre, University Health Network, Canada
- 17:05 S8.06 - Novel Bispecific IO Agents**
Sarah Goldberg, Yale Cancer Center, United States
- 17:15 S8.07 - Other Immunomodulatory Agents**
Melissa Johnson, Sarah Cannon Research Institute, United States
- 17:25 Panel Discussion:**
Thomas Marron, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, United States
Andrew Chow, Memorial Sloan Kettering Cancer Center, United States
Jhanelle Gray, Moffitt Cancer Center, United States
David Carbone, The Ohio State University Comprehensive Cancer Center, United States
Sandip Patel, University of California San Diego, United States
Jonathan Riess, University of California Davis Comprehensive Cancer Center, United States
- 17:55 Session 8: Debate**
- S8D.01 - Patients Completing 2 Years of IO Therapy Should Continue IO - Yes**
Estelamari Rodriguez, Sylvester Cancer Center, University of Miami, United States
- S8D.02 - Patients Completing 2 Years of IO Therapy Should Continue IO - No**
Hossein Borghaei, Fox Chase Cancer Center, United States

18:15 – 18:30

Registration and Dinner

18:30 – 19:30

CME/MOC Credit - Peer Pressure: How Well Do You Know Your ADCs? Answers to Key Questions About Antibody–Drug Conjugates in NSCLC
This activity is supported by independent educational grants from AstraZeneca and Daiichi Sankyo, Inc.

Starlight Ballroom



DINNER PROVIDED



LIVE-STREAMED SESSION

Chair: Benjamin Levy, Johns Hopkins, United States

Presenters: Stephen Liu, Georgetown University, United States,
Melissa Johnson, Sarah Cannon Research Institute, United States

Welcome, Introduction, and Setting the Stage for the ADC Challenge

The ADC Challenge: Key Questions and Insightful Answers About the Growing Role and Impact of ADCs Targeting HER2, HER3, TROP2, CEACAM5, MET, and others in NSCLC

Q&A, Reflections, and Conclusions

19:30 – 22:00

Faculty Dinner including Faculty Keynote by Corey Langer: FK01 - 35 Years in the Trenches in Thoracic Oncology: My Precarious Journey from Nihilism to Hope

Wedgewood Ballroom

BY INVITATION ONLY

04 | PROGRAM

SATURDAY, FEBRUARY 25



Registration Desk Opening Hours: **06:30 – 12:00**



Wedgewood Foyer



06:30 – 08:00 Networking Breakfast
Wedgewood Ballroom



**BREAKFAST
WILL BE PROVIDED**

08:15 – 09:55

Session 9: Therapy for Early Stage

Starlight Ballroom

LIVE-STREAMED SESSION

Chairs: Sonam Puri, Huntsman Cancer Institute at the University of Utah, United States
David Harpole, Duke University, United States

08:15

S9.01 - Adjuvant CT/IO

Jonathan Spicer, McGill University Health Center, Canada

08:25

S9.02 - Neoadjuvant CT/IO

Patrick Forde, Johns Hopkins University, United States

08:35

S9.03 - Adjuvant TKI

Jonathan Goldman, University of California, Los Angeles, United States

08:45

S9.04 - Neoadjuvant TKI

Jamie Chافت, Memorial Sloan Kettering Cancer Center, United States

08:55

S9.05 - SBRT + Systemic Therapy for Early Stage

Jeffrey Bradley, Emory University, United States

09:05

S9.06 - Trials Based on ctDNA

Max Diehn, Stanford University, United States

09:15

Panel Discussion:

Narjust Florez, Dana-Farber Cancer Institute, United States

Erin Gillaspie, Vanderbilt University Medical Center, United States

Jason Porter, West Cancer Center, United States

Raymond Osarogiagbon, Baptist Cancer Center, United States

Sheena Bhalla, University of Texas Southwestern Medical Center, United States

Jay Lee, University of California, Los Angeles, United States

09:45

Session 9: Debate

S9D.01 - Adjuvant Immunotherapy Should Be Used Regardless of PDL1 - Yes

Marina Garassino, University of Chicago, United States

S9D.02 - Adjuvant Immunotherapy Should Be Used Regardless of PDL1 - No

Heather Wakelee, Stanford University, United States



09:55 – 10:30 Networking Break
Starlight Foyer



**REFRESHMENTS
WILL BE PROVIDED**

SATURDAY, FEBRUARY 25, 2023

04 | PROGRAM

SATURDAY, FEBRUARY 25

SATURDAY, FEBRUARY 25, 2023

10:30 - 12:10

Session 10: Antibody Drug Conjugates

Starlight Ballroom

▶ LIVE-STREAMED SESSION

Chairs: Kamya Sankar, Cedars-Sinai Medical Center, United States

Suresh Ramalingam, Winship Cancer Institute of Emory University, United States

10:30

S10.01 - Predictive Biomarkers of ADCs

David Kozono, Dana-Farber Cancer Institute, United States

10:40

S10.02 - MET Targeted ADCs

D. Ross Camidge, University of Colorado, United States

10:50

S10.03 - Trop2 Targeted ADCs

Benjamin Levy, Johns Hopkins, United States

11:00

S10.04 - Toxicity of ADCs

Saama Waqar, Washington University School of Medicine in St. Louis, United States

11:10

S10.05 - ERBB Family Targeted ADCs

Conor Steuer, Emory, United States

11:20

S10.06 - Emerging ADC Targets

Lova Sun, University of Pennsylvania, United States

11:30

Panel Discussion:

Kurt Schalper, Yale University, United States,

Alex Adjei, Cleveland Clinic, United States,

Misako Nagasaka, University of California, Irvine, United States,

Mary Jo Fidler, Rush University, United States,

Jared Weiss, UNC Lineberger Comprehensive Cancer Center, United States

12:00

Session 10: Debate

S10D.01 - For Any Patient Being Considered for an ADC, an IHC Test Should Be Performed to Assess Expression of the Target - Yes

Ignacio Wistuba, MD Anderson Cancer Center, United States

S10D.02 - For Any Patient Being Considered for an ADC, an IHC Test Should Be Performed to Assess Expression of the Target - No

Sanja Dacic, Yale School of Medicine, United States

12:10 - 12:15

Wrap Up and Close

Starlight Ballroom

▶ LIVE-STREAMED SESSION



5

POSTERS


05 | POSTER LISTINGS

 **Venue:** Wedgewood Ballroom

POSTER DISPLAY TIMES:	THURSDAY, FEBRUARY 23	06:30 – 18:30
	FRIDAY, FEBRUARY 24	06:30 – 15:30
POSTER PRESENTER QUESTION TIME:	THURSDAY, FEBRUARY 23	17:25 – 18:25

- P01** **Changes in PD-L1 Expression and Tumor Mutational Burden Between Paired Samples and Relationship to Immune Checkpoint Inhibitor Outcomes in Patients with Non-Small Cell Lung Cancer**
Alessandro Di Federico, Dana-Farber Cancer Institute, United States
- P02** **MET Exon 14 Skipping Mutation in Non-Small Cell Lung Cancer (NSCLC): An Analysis by Specific Mutation, Histology, and Smoking Status**
Jennifer A. Marks, Georgetown University, United States
- P03** **Lung Cancer Approved Tyrosine Kinase Inhibitors That Inhibit MATE-1 can Lead to “False” Decreases in Renal Function**
Monica Chen, MSKCC, United States
- P04** **Impact of STK11 and/or KEAP1 Deletion on Outcomes to Immunotherapy in Non-Small Cell Lung Cancer**
Malini Gandhi, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, United States
- P05** **Genomic And Immunophenotypic Landscape Of Acquired Resistance (AR) To PD-(L)1 Blockade In Non-Small Cell Lung Cancer**
Biagio Ricciuti, Dana-Farber Cancer Institute, United States
- P06** **Real World Outcomes of Lurbinectedin as Second Line Treatment in Extensive Stage-Small Cell Lung Cancer (ES-SCLC)**
Aakash Desai, Mayo Clinic, United States
- P07** **Co-occurring Alterations in Multiple Tumor Suppressor Genes are Associated with Worse Outcomes in Patients with EGFR-Mutant Lung Cancer**
Paul Stockhammer, Yale School of Medicine, United States
- P08** **Pivotal Data Update from the Phase 1/2 TRIDENT-1 Trial of Repotrectinib in Patients with ROS1+ Advanced Non-Small Cell Lung Cancer (NSCLC)**
Guilherme Harada, Memorial Sloan Kettering Cancer Center, United States
- P09** **Activating MET Kinase Domain Mutations Define a Novel Targetable Molecular Subtype of Non-Small Cell Lung Cancer That is Clinically Sensitive to MET Inhibitor Elzovantinib (TPX-0022)**
Federica Pecci, Lowe Center for Thoracic Oncology, Dana-farber Cancer Institute, United States
- P10** **Impact of Aneuploidy and Chromosome 9p Loss on Tumor Immune Microenvironment and Immune Checkpoint Inhibitor Efficacy in Non-small Cell Lung Cancer**
Joao Alessi, Dana-Farber Cancer Institute, United States
- P11** **A Phase 1 Trial of BI 1810631, a HER2 Tyrosine Kinase Inhibitor (TKI), as Monotherapy in Patients with Advanced/Metastatic Solid Tumors with HER2 Aberrations**
Hibiki Udagawa, The University of Texas MD Anderson Cancer Center, United States

- 
- P12 Activity of Gilteritinib in Resistant ROS1 Rearranged Non-Small Cell Lung Cancer**
Rajat Thawani, Oregon Health & Science University, United States
- P13 MDM2 Inhibition in Combination with MEK Inhibition in Pre-clinical Models of Lung Adenocarcinomas with MDM2 Amplification**
Arielle Elkrief, Memorial Sloan Kettering Cancer Center, United States
- P14 Differentiating Ensartinib from Lorlatinib and Alectinib for First Line Use in an ALK+ Non-Small Cell Lung Cancer Preclinical Model (ResCu)**
Christopher Bulow, ResistanceBio, United States
- P15 Efficacy and Safety of Larotrectinib in Patients with Tropomyosin Receptor Kinase (TRK) Fusion Lung Cancer by Prior Line of Systemic Therapy and Performance Status**
Matteo Repetto, Memorial Sloan Kettering Cancer Center, United States
- P16 Targetable Molecular Algorithm and Training Pathways Development for Treatment of the Non-Small Cell Lung Cancer**
Ayesha Munir, Medstar Georgetown Cancer Institute, United States
- P17 Clinical and Genomic Predictors of Response and Toxicity to Sotorasib in a Real-World Cohort of Patients with Advanced KRAS G12C-Mutant Non-small Cell Lung Cancer**
Rohit Thummalapalli, Memorial Sloan Kettering Cancer Center, United States
- P18 Phase II Trial of Regorafenib and Oral Methotrexate in Previously Treated Advanced KRAS Mutant Non-Small Cell Lung Cancer**
Jacqueline Aredo, Stanford Cancer Institute, United States
- P19 IDH1 and IDH2 Mutations in Non-small Cell Lung Cancer (NSCLC)**
Lacey Williams, Georgetown University, United States
- P20 Prognostic and Predictive Relevance of 3q Amplification in Squamous Cell Carcinoma of the Lung**
Fawzi Abu Rous, Henry Ford Health, United States
- P21 HER2/ERBB2 Mutations in Metastatic Non-Small Cell Lung Cancer – Prevalence, Real-World Treatment Patterns and Outcomes from a Clinico-Genomic Database**
Sarah Waliany, Stanford University School of Medicine, United States
- P22 Mutations in Spliceosome Genes, SRSF2 and FUBP1, in NSCLC Are Associated with Multiple Actionable Driver Mutations, Notably KRAS G12C/V and EGFR L858R as Well as STK11/KEAP1 Mutations without Actionable Driver Mutations. Results Collected from a Survey of cBioPortal GENIE Database**
Alexandria Lee, University of California Irvine School of Medicine Department of Internal Medicine, United States
- P23 Mutations in the RNA Binding Motif Protein 10 (RMB10) in NSCLC Are Highly Associated with Multiple Actionable Driver Mutations in Particular EGFR L858R or KRAS G12C. Results from a Survey of the Cbioportal GENIE Database**
Danielle Brazel, University of California Irvine, United States
- P24 Plasma PCSK9 Levels in Patients Receiving Neoadjuvant Pembrolizumab in Resectable Non-Small Cell Lung Cancer (NSCLC)**
Cameron Wood, Duke University Health System, United States
- P25 Fibroblast Growth Factor Receptor (FGFR) Aberrations in Metastatic Non-Small Cell Lung Cancer (mNSCLC): An Analysis of Prevalence and a Potential Therapeutic Target for Resistance to Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR TKIs)**
Karan Jatwani, Roswell Park Comprehensive Cancer Center, United States

- 
- P26 **Out of Pocket Costs and Receipt of Financial Assistance for Patients with Lung Cancer Prescribed an Oral Targeted Therapy at an Academic Medical Center**
Meera Ragavan, University of California, San Francisco, United States
- P27 **Clinicogenomic Characteristics of EGFR-Mutant Non-Small Cell Lung Carcinoma with CNS Metastases**
Jane Sze Yin Sui, Memorial Sloan Kettering Cancer Center, United States
- P28 **Inhibition of ATR Can Target Osimertinib Resistance in EGFR-Mutated NSCLC**
Benjamin Herzberg, Columbia University Medical Center, United States
- P29 **The LAG-3/FGL1 Axis is a Dominant Immune Evasion Pathway in NSCLC Modulated by Hypoxia**
Maria Villalba Esparza, Yale University, United States
- P30 **NRG1 Fusions in Non-Small Cell Lung Cancer (NSCLC)**
Muneeb Rehman, Georgetown University, United States
- P31 **GUK1 is a Novel Metabolic Liability in Oncogene-Driven Lung Cancer**
Jaime Schneider, Massachusetts General Hospital, United States
- P32 **Durable Complete Response in Leptomeningeal Disease (LMD) of EGFR Mutated Non-Small Cell Lung Cancer (NSCLC) to Amivantamab, an EGFR-MET Receptor Bispecific Antibody, After Progressing on Osimertinib**
Yoonhee Choi, New York-Presbyterian of Queens, United States
- P33 **SMARCA4-deficient Undifferentiated Lung Carcinoma with Additional Microsatellite Instability Mixed Response to Pembrolizumab Followed by Hyperprogression – A Cautionary Tale Highlighting the Pitfalls to Tumor Agnostic Drug Approvals**
Elizabeth Burns, University of Florida, United States
- P34 **BASECAMP-1: Leveraging Human Leukocyte Antigen A (HLA-A) Loss of Heterozygosity (LOH) in Solid Tumors by Next-Generation Sequencing (NGS) to Identify Patients With Relapsed Solid Tumors for Carcinoembryonic Antigen (CEA) and Mesothelin (MSLN) Logic-Gated**
Caleb Smith, Mayo Clinic, United States
- P35 **A Case and the Landscape of Coexisting EGFR Mutation in Non-Small Cell Lung Cancer (NSCLC) with Microsatellite Instability (MSI) High and Tumor Mutation Burden (TMB) High Traits**
Leeseul Kim, Ascension Saint Francis Hospital, United States



6

INDUSTRY
SUPPORTERS

06 | INDUSTRY SUPPORTERS

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7

GENERAL INFORMATION

HEALTH & SAFETY MEASURES

IASLC recommends that all in-person attendees are fully vaccinated against COVID-19 by the time of the Meeting. Fully vaccinated refers to completing the approved first 2 vaccines, as per the guidelines of their country of residence. IASLC will, however, not require proof of vaccination prior to or during the Meeting.

MASKS AND FACE COVERINGS

Masks will be encouraged to be worn at TTLC 2023.

By registering to attend, you agree that:

You will not attend if you have any COVID-19 symptoms.

If during your attendance you develop any COVID-19 symptoms, you will immediately:

- Self-isolate;
- Comply with all local/national government restrictions; and
- Inform the TTLC 2023 Conference Secretariat by email (TTLC2023-registration@icsevents.com).

ACCESS / SECURITY

Attendees are requested to wear their name badges at all times in order to participate in the Scientific Sessions and Exhibition. A 50 USD fee applies for any name badge reprints due to lost name badges.

OPENING HOURS

REGISTRATION

Wednesday, February 22

15:00 – 20:30

Lobby Lounge

Thursday, February 23

06:30 – 18:00

Wedgewood Foyer

Friday, February 24

06:30 – 18:00

Wedgewood Foyer

Saturday, February 25

06:30 – 12:00

Wedgewood Foyer



OPENING HOURS

NETWORKING BREAKFAST, LUNCH & BREAKS

	Breakfast Wedgewood Ballroom	AM Break Starlight Foyer	Lunch Driveway under the FIG Tree and Wedgewood Ballroom	PM Break Starlight Foyer
Thursday, February 23	06:30 - 08:00	10:20 - 10:45	12:25 - 13:30	15:20 - 15:45
Friday, February 24	06:30 - 08:00	09:55 - 10:30	13:10 - 14:15	15:45 - 16:15
Saturday, February 25	06:30 - 08:00	09:55 - 10:30	N/A	N/A

EXHIBIT HOURS

📍 Starlight Foyer

Wednesday, February 22	17:00 - 18:30
Thursday, February 23	10:00 - 16:00
Friday, February 24	09:30 - 18:30
Saturday, February 25	09:30 - 12:30

POSTER DISPLAY TIMES

📍 Wedgewood Ballroom

Thursday, February 23	06:30 - 18:30
Friday, February 24	06:30 - 15:30

LIVESTREAM & RECORDINGS (VIRTUAL PLATFORM)

All sessions will be livestreamed, and video recorded. Recordings will be made available on the Virtual Platform within 24 hours. Virtual delegates can participate in the Q&A via the chat on the Virtual Platform.

The Virtual Platform also includes presentations slides, abstracts, and electronic versions of most posters. Log-in details including passwords were sent to your registered email in the Final Registration Confirmation email. If you need assistance, please contact:

TTL2023-Registration@icsevents.com.

Access to TTL2023 Virtual Platform at: <https://ttl23-iaslc.junolive.co/>

CERTIFICATE OF ATTENDANCE & ACCREDITATION

Delegates can download their 'Certificate of Attendance' after completing the online meeting evaluation form sent to you by email at the conclusion of the Meeting.

The IASLC TTL2023 is not accredited and does not provide CME credits or certifications for attending sessions.

WIFI

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Lost and found items should be returned / claimed at the Registration Desk.



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The **IASLC Patient Advocate Educational Awards** provide an opportunity for patients/survivors, carers/caregivers, and patient advocates to be a part of IASLC's most anticipated global conference: the IASLC World Conference on Lung Cancer (WCLC). The number of educational awards shall be limited to a maximum of five. Fewer than the maximum amount may be awarded, depending on interest, qualifications of the applicants, and the review process.

APPLICATIONS
ACCEPTED:
**March 8 –
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Eligibility:

Special consideration will be given to applicants who have never been awarded a WCLC Patient Advocate Educational Award (formerly, the WCLC Patient Advocate Travel Award) and who are relatively new to lung cancer patient advocacy. We are seeking qualified applicants who show a high level of interest in patient advocacy, would benefit from in-person attendance at WCLC, and are working on a project that will have a positive impact in the lung cancer community.

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INTERNATIONAL
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Journal of Thoracic Oncology

Official Journal of the International Association for the Study of Lung Cancer

Editor-in-Chief: **Alex A. Adjei**, MD, PhD, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA

The **Journal of Thoracic Oncology (JTO)**, the official journal of the International Association for the Study of Lung Cancer, is the primary educational and informational publication for topics relevant to detection, prevention, diagnosis, and treatment of thoracic malignancies. JTO emphasizes a multidisciplinary approach, and includes original research (clinical trials, and translational or basic research), reviews, and opinion pieces. The audience consists of epidemiologists, medical oncologists, radiation oncologists, thoracic surgeons, pulmonary specialists, radiologists, pathologists, and research scientists with a special interest in thoracic oncology.



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8

ABSTRACTS

Congratulations to our oral presenters for receiving the TTLC 2023 Education Award!

BEST FELLOWS ORAL ABSTRACT SESSION

OA01.01: Impact of Baseline Clinicopathologic and Genomic Features on Outcomes to KRAS G12C Inhibitors in Patients with NSCLC

Dr. Giuseppe Lamberti¹, Dr. Alissa J. Cooper², Dr. Biagio Ricciuti¹, Dr. Joao V. Alessi¹, DR. Adriana P. de Castro Barrichello¹, Dr. Federica Pecci¹, Dr. Victor Vaz¹, Dr. Shu-Chi Tseng^{3,4}, Dr. Subba R. Digumarthy², Dr. Pasi A. Jänne¹, Dr. Mizuki Nishino³, Dr. Lynette M. Sholl⁵, Dr. Rebecca Heist², Dr. Mark Awad¹, ¹Lowe Center for Thoracic Oncology - Dana-Farber Cancer Institute, Boston, United States, ²Massachusetts General Hospital Cancer Center, Boston, United States, ³Department of Radiology, Brigham and Women's Hospital, Boston, United States, ⁴Department of Medical Imaging and Intervention, Chang Gung Memorial Hospital at Linkou and Chang Gung University, Taoyuan, Taiwan, ⁵Department of Pathology, Brigham and Women's Hospital, Boston, United States

BACKGROUND

Baseline factors that influence efficacy of KRASG12C inhibitors (G12Ci) in patients with KRASG12C-mutant non-small cell lung cancer (NSCLC) are largely unknown. We sought to identify clinicopathological and genomic features associated with outcome to G12Ci.

METHODS

Among patients at the Dana-Farber Cancer Institute and Massachusetts General Hospital with NSCLC who received a G12Ci as monotherapy, baseline clinicopathological and genomic features were correlated with objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). Genomic alteration pathogenicity for STK11, KEAP1, TP53, ATM, SMARCA4, and CDKN2A was assessed using OncoKB, COSMIC, and PolyPhen-2. The sum of baseline diameters (SBD) was obtained by blinded radiology review by totaling target lesion longest diameters measured according to RECIST v1.1 criteria.

RESULTS

One hundred patients received a G12Ci (median age 67 years, 64% women): 24 (24%) had an Eastern Cooperative Oncology Group performance status (ECOG PS) ≥ 2 , 46 (46%) had history of brain metastases prior to G12Ci start, of which 15 (33%) were untreated before G12Ci initiation. In the whole cohort, the ORR was 31.9% (N=30/94), the median PFS (mPFS) was 5.4 months (95%CI:4.1-6.5), and the median OS (mOS) was 9.8 months (95%CI:7.9-16.3), with a median follow-up time of 12.8 months (95%CI:9.9-19.4). Compared to an ECOG PS of 0-1, an ECOG PS of ≥ 2 was associated with similar ORR (36.5% vs 15.0%; p=0.103), but a shorter mPFS (5.9 vs 3.3 months, HR:2.31; p=0.002) and mOS (13.0 vs 4.9 months, HR: 3.18; p<0.001). Receipt of a G12Ci in the 1st-line setting was associated with a higher ORR (69.2% [N=9/13] vs 25.9% [N=21/81]; p=0.003), and a significantly longer mPFS (not reached vs 4.8 months, HR:3.04; p=0.009), and mOS (not reached vs 8.8 months. HR:5.71; p=0.016), compared to receipt of a G12Ci in the ≥ 2 nd line. Compared to a low SBD (defined as less than the median SBD of 6.2 cm, range: 1.0 – 35.0), a high SBD was associated with shorter mPFS (6.5 vs 3.9 months, HR:2.86; p<0.001) and mOS (18.9 vs 5.9 months, HR:3.82; p<0.001).

Among NSCLCs with available genomic sequencing information, co-occurring genomic alterations included STK11 mutation (mut) in 27 cases (28.1%), KEAP1 mut in 19 (24.7%), TP53 mut in 43 (43.9%), SMARCA4 mut in 10 (13.3%), ATM mut in 13 (14.0%), and CDKN2A deletion in 24 (26.1%). STK11 mut compared to STK11 wild-type (wt) had shorter mPFS (5.9 vs 3.9 months, HR: 1.85; p=0.022), but no difference in ORR or mOS. Longer mPFS and mOS were observed in

KEAP1 wt compared to KEAP1 mut (mPFS: 5.6 vs 2.7 months, HR: 2.30; p=0.02; mOS: 13.0 vs 5.7 months, HR: 2.20; p=0.014). After adjusting for potential confounding factors, shorter PFS was associated with KEAP1 mut (HR:2.34; p=0.04) and high SBD (HR:2.27; p=0.02), while shorter OS was associated with ECOG PS \geq 2 (HR:3.22; p=0.016), treatment line \geq 2nd (HR:10.42; p=0.024), and high SBD (HR:3.55; p=0.003).

CONCLUSION

Baseline clinicopathological characteristics may help predict outcome to G12Ci in patients with KRASG12C mutant NSCLC. Larger series are needed to confirm if co-occurring genomic alterations may help identify pts who derive differential benefit from G12Ci.

OA01.02: CNS Metastases in KRAS G12D-Mutant Non-Small Cell Lung Cancer: Frequency and Associated Clinicopathologic Factors

Dr. Alissa Cooper¹, Dr. Jochen Lennerz¹, Dr. Farhaana Narinesingh¹, Dr. Mari Mino-Kenudson¹, Dr. Yin Hung¹, Dr. Zofia Piotrowska¹, Dr. Ibiayi Dagogo-Jack¹, Dr. Lecia Sequist¹, Dr. Justin Gainor¹, Dr. Jessica Lin¹, Dr. Rebecca Heist¹
¹Massachusetts General Hospital/Harvard Medical School, Boston, United States

BACKGROUND

Central nervous system metastases (CNS mets) represent a significant clinical problem in non-small cell lung cancer (NSCLC), typically portending poor prognosis and treatment outcome. Clinical and genomic variables associated with CNS mets in NSCLC harboring KRAS G12D mutations – a subtype of lung cancer for which targeted therapies (G12D-specific inhibitors) are emerging – remain unknown.

METHODS

This was a single institution retrospective study of patients (pts) with KRAS G12D-mutant NSCLC detected by the Massachusetts General Hospital SNaPshot next-generation sequencing assay. Clinical and pathologic characteristics, including co-mutations STK11, KEAP1, and TP53, were reviewed, and Cox regression analysis was performed on relevant variables to determine association with the occurrence of CNS mets during disease course.

RESULTS

107 pts had KRAS G12D-mutant NSCLC, among whom 75 had metastatic disease. Median age was 68 (range 29 - 90), and 59.8% were female. Most patients were former smokers (80, 74.8%) with median pack-years of 25. 51 pts had presented with stage IV disease at initial diagnosis (47.7%); the remaining 24 pts developed metastatic disease following initial diagnosis. The incidence of CNS mets at initial diagnosis of metastatic KRAS G12D-mutant NSCLC was 25.3% (19/75), while the cumulative incidence of CNS mets was 36.0% (27/75). On univariate analysis, PD-L1 TPS 1-49% (HR = 3.500 (95% CI 1.2259 – 10.0071, p = 0.0181)), and TP53 co-mutation (HR 2.8392 (95% CI 1.1560 – 7.0820, p = 0.0231)) were associated with CNS mets, while sex, race, smoking status, STK11, KEAP1, and SMARCA4 co-mutations were not. On multivariate analysis, only TP53 co-mutation (HR = 3.2491 (95% CI 1.0946 – 10.1611, p = 0.03621)) was independently associated with the presence of CNS mets.

CONCLUSION

CNS mets are common in KRAS G12D-mutant NSCLC. Only TP53 co-mutation was independently associated with the presence of CNS mets in this patient population.

OA01.03: First-line Osimertinib in Patients with Uncommon EGFR-Mutated Non-Small Cell Lung Cancer

Miss Tia Cheunkarndee¹, Matthew Guo¹, Dr. Stefanie Houseknecht¹, Dr. Josephine Feliciano¹, Dr. Christine Hann¹, Dr. Vincent Lam¹, Dr. Benjamin Levy¹, Dr. Joseph Murray¹, Dr. Julie Brahmer¹, Dr. Patrick Forde¹, Dr. Kristen Marrone¹, Dr. Susan Scott¹, ¹Johns Hopkins University School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, United States

BACKGROUND:

Osimertinib, a third-generation tyrosine kinase inhibitor (TKI), has led to improved outcomes for patients with non-small cell lung cancer (NSCLC) harboring classic epidermal growth factor receptor (EGFR) mutations. However, 15-20% of patients whose tumors have EGFR mutations have non-classic, or uncommon, mutations, including several less common EGFR exon 19 deletions and compound mutations. To date, relatively little is known about the efficacy of osimertinib in these patients.

METHODS:

Patients who received first-line osimertinib and harbored uncommon EGFR mutations (defined as non-E746_A750del, non-L858R, non-T790M, non-ex20ins) were included in the study cohort. Patients whose tumors possessed compound mutations including both a classical and uncommon mutation were included if the uncommon mutation was within the kinase domain of EGFR. Treatment response assessment and time to progression from the start of osimertinib were abstracted from clinical records based on radiographic reports and treating provider's clinical assessment. Kaplan-Meier survival analyses were used to estimate progression-free survival (PFS) and overall survival (OS).

RESULTS:

Uncommon EGFR mutations were identified in 18% (n=26) of 144 consecutive patients initiated on first line osimertinib for stage III/IV EGFR-mutated NSCLC at Johns Hopkins from November 2016 to August 2021. Of these, 69% were female, median age was 65, 35% had a smoking history, 92% presented with stage IV cancer, and 96% of tumors were adenocarcinoma histology. The most common metastatic sites at diagnosis included bone (65%), contralateral lung or pleura (58%), and brain (58%). Among all 26 patients, partial response was observed in 85% (n=22) including all tumors with compound mutations, and only one patient experienced disease progression as best response (Table). One-year PFS was 46%. Median PFS and median OS were 11 months (95% CI 9-16) and 35 months (95% CI 22-not reached), respectively, with a median follow up of 29 months. The most common sites of progression included the lung (54%), lymph nodes (31%), and brain (27%). Six patients continued on first-line osimertinib with the addition of radiation therapy for oligoprogressive disease (Table).

CONCLUSION:

Overall, osimertinib exhibited favorable efficacy in patients whose tumors possessed uncommon EGFR mutations, and this cohort contributes to the growing body of literature reporting treatment outcomes for these non-classical variants. The wide array of mutations expressed in this group and varied duration of treatment responses underscore the need for further investigation into the optimal first-line therapy for each specific EGFR mutation.

Table: Treatment response and outcomes by *EGFR* Mutation

EGFR Mutation	Sex	Age	Smoking History	Best Overall Response	PFS (months)	Time on First-Line Osimertinib (months)	OS (months)
Exon 18 E709_T710delinsD	M	65	N	PD	2.3	4.1	9.3
Exon 18 G719A	F	79	Y	SD	10	11	14
Exon 19 E746_S752delinsV, Patient 1	M	54	Y	SD	4.8	6.0	16*
Exon 19 E746_S752delinsV, Patient 2	M	66	N	PR	15	19	34
Exon 19 E746_S752delinsV, Patient 3	F	69	N	PR	46*	46	46*
Exon 19 E746_S752delinsV, Patient 4	F	50	N	PR	13	18	24*
Exon 19 E746_T751delinsP	F	89	N	PR	27	36^	36*
Exon 19 L747_A750delinsP	M	64	N	SD	13	13	16*
Exon 19 L747_P753delinsS	F	61	N	PR	14*	14	14*
Exon 19 L747_T751del, Patient 1	F	58	N	PR	4.8	5.0	10
Exon 19 L747_T751del, Patient 2	M	78	Y	PR	9.6	17	35
Exon 19 L747_T751del, Patient 3	F	56	N	PR	4.9	40^	40*
Exon 19 L747_T751delinsP	M	66	N	PR	17	22	22
Exon 19 L747P	F	90	Y	PR	11	10	11
Exon 21 L861Q	F	62	Y	PR	30	31	31*
EGFR Compound Mutation							
Exon 18 G719A, Exon 18 K714E	F	64	N	PR	4.4	5.4	32*
Exon 18 G719A, Exon 20 S768I	F	68	Y	PR	16	29^	29
Exon 18 G719C, Exon 18 E709V	F	52	N	PR	26*	26	26*
Exon 18 G719S, Exon 20 S768I	F	58	N	PR	8.8	36^	36
Exon 18 G724S, Exon 20 S752_I759del	F	54	N	PR	7.7	19^	35*
Exon 18 L718Q, Exon 20 C797S (de novo)	F	68	N	PR	8.8	12	12
Exon 19 E746_E749del, Exon 20 T790M	F	32	Y	PR	11	22	56
Exon 21 L858R, Exon 20 S768I	F	89	Y	PR	20	19	20
Exon 21 L858R, Exon 21 V834L	M	74	Y	PR	25	26	33
Exon 21 L858R, Exon 21 V834L, Exon 20 C797S (de novo)	F	75	N	PR	11	32^	50
Exon 21 L858M, Exon 21 L861Q	F	46	N	PR	6.1	7.6	20

*Patient has maintained progression free survival and/or is alive at end of data collection

^Patient continued on first-line osimertinib with the addition of radiation therapy for oligoprogressive disease

OA01.04: Risk of Further Progression or Death among Durable Progression-Free Survivors with Non-Small Cell Lung Cancer in PD-1 Blockade Trials: Guidance on Imaging Surveillance Interval

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BACKGROUND:

Durable progression-free survivors (dPFSors) over 2 years have been reported among non-small cell lung cancer (NSCLC) patients treated with PD-1 blockade. However, non-negligible risk of further progression still exists and the optimal imaging surveillance interval is unknown. Currently there is no guideline recommendation addressing this issue. It is also challenging to conduct a clinical trial to answer this important clinical question. This study aims to describe the risk of further progression or death (P or D) among dPFSors to guide imaging surveillance.

METHODS:

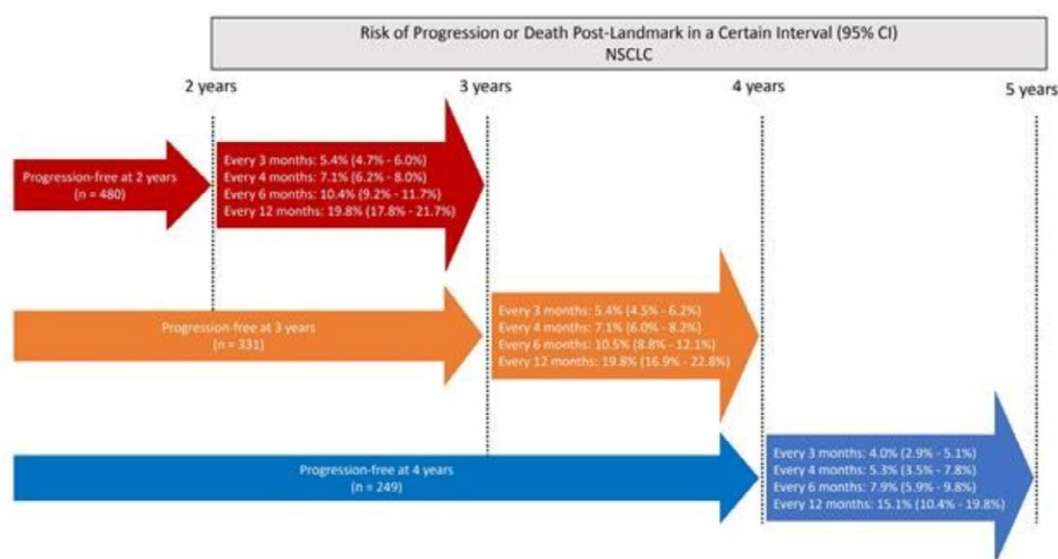
Published anti-PD(L)1 clinical trials with follow-up of at least 5 years were included. Individual patient data of progression-free survival (PFS) were extracted. Patients with PFS of at least 24 months was considered as dPFSors. Conditional risks of progression/death (P/D) every 3, 4, 6, and 12 months in each subsequent year were calculated with 95% confidence interval (CI). We pre-specified three maximal risk levels – 10%, 15%, and 20% at each imaging scanning interval. An interval is considered as acceptable if the 95% CI upper bound of the risk at each scan is lower than a pre-specified risk level.

RESULTS:

A total of 7 trials with 3115 patients were included (Checkmates 017, 057, 227 and Keynotes 024, 010, 189, 407), of whom 480 (15.4%) were exceptional responders. Among those patients, the PFS probability for additional 3 years was 49.9% (95% CI, 45.2% - 55.0%). The quarterly risk of P/D was significantly lower than 6.5%. The pooled yearly risk was 19.8% (17.8% - 21.7%), 19.8% (16.9% - 22.8%), and 15.1% (10.4% - 19.8%), at 2, 3, and 4 years respectively (Details in Figure 1). Under risk at 10%, 15%, and 20%, dPFSors can be scanned every 4, 6, and 6 months during the third year, every 4, 6, and 6 months during the fourth year, and every 6, 6, and 12 months during the fifth year, respectively.

CONCLUSION:

The quarterly risk of P or D is extremely small, < 6.5%, supporting extending imaging surveillance beyond every 3 months among dPFSors. However, about half of the dPFSors may still progress in the following 3 years. Our findings allow clinicians and patients make data-driven decisions on imaging surveillance intervals, based on their own risk tolerance level.



08 | ABSTRACTS POSTER SESSIONS

P01: Changes in PD-L1 Expression and Tumor Mutational Burden between Paired Samples and Relationship to Immune Checkpoint Inhibitor Outcomes in Patients with Non-Small Cell Lung Cancer

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BACKGROUND

Programmed cell death receptor ligand 1 (PD-L1) tumor proportion score (TPS) and tumor mutational burden (TMB) are key biomarkers of response to immunotherapy in non-small cell lung cancer (NSCLC). Data on their variations across samples in the same patient are limited. Here we sought to identify correlates of PD-L1 and TMB changes and their impact on outcomes in NSCLC.

METHODS

Patients with NSCLC and ≥ 2 samples that underwent PD-L1 TPS assessment by immunohistochemistry and/or TMB evaluations by next-generation sequencing at the Dana-Farber Cancer Institute were included. In patients with > 2 samples, each sample was paired with its subsequent and each pair was analyzed independently. Absolute changes in PD-L1 expression of 10-49% and 50-100% were defined as minor or major, respectively. Major variation in TMB was defined as change of ≥ 2 quartiles. Outcomes of patients who received immune checkpoint inhibitors (ICI) after ≥ 2 PD-L1 or TMB assessments were analyzed. PD-L1 was characterized as "discordant" if ≥ 1 PD-L1 TPS prior to ICI was negative ($< 1\%$) and ≥ 1 was positive ($\geq 1\%$).

RESULTS

406 paired samples were included in the PD-L1 cohort (median PD-L1: 0; range: -90,+95%) and 414 in the TMB cohort (median TMB: 0 mut/Mb; range: -20.6,+24.5). Concordance between samples was high for both PD-L1 ($R=0.53$, $P<0.0001$) and TMB ($R=0.80$, $P<0.0001$). Samples taken within < 1 year vs ≥ 1 year apart showed higher concordance in PD-L1 ($P=0.006$), but not in TMB ($P=0.72$). Major changes in PD-L1 expression were observed in 18.0% of cases (major increase: 9.6%; major decrease: 8.4%); minor changes occurred in 29.3% of cases (minor increase: 14.3%; minor decrease 15.0%). After dividing TMB into quartiles, 60.9% of samples did not show any change to different quartiles, 30.9% showed a change by one quartile and 8.2% by ≥ 2 quartiles. PD-L1 levels, but not TMB, decreased between samples with intervening ICI therapy ($P=0.04$).

Acquired copy loss of CD274, PDCD1LG2, JAK2, MAP2K1 and B2M genes were significantly enriched among samples with decrease in PD-L1 expression ($Q<0.15$). At least one gene among CD274, PDCD1LG2, JAK2, MAP2K1, B2M, STK11, KEAP1, SMARCA4, CDKN2A/B and TP53 showed acquired copy number loss in 7/9 (78%) cases with major decrease in PD-L1 TPS and acquired copy number gain in 8/10 (80%) cases with major increase in PD-L1 TPS.

Among 26 patients (41.2% of those treated with ICI after ≥ 2 PD-L1 assessments) with discordant PD-L1 expression (i.e. one positive and one negative sample), cases where the last PD-L1 TPS prior to immunotherapy was $\geq 1\%$ achieved significantly longer progression-free survival (adjusted HR 0.26; 95%CI, 0.09-0.78; $P=0.02$) and overall survival (adjusted HR 0.27; 95%CI, 0.08-0.96; $P=0.04$) compared with those with a negative PD-L1 level prior to immunotherapy. No difference was found in outcomes according to TMB variation.

CONCLUSION

Although there is generally good concordance in PD-L1 and TMB between paired NSCLC samples, major variations in these biomarkers occurred in 18.0% and 8.2% of cases, respectively. Changes in PD-L1 expression are associated with acquired genomic alterations, and PD-L1 assessment just prior to immunotherapy administration might be a more accurate predictor of response compared to older samples.

P02: MET Exon 14 Skipping Mutation in Non-Small Cell Lung Cancer (NSCLC): An Analysis by Specific Mutation, Histology, and Smoking Status

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BACKGROUND

The diverse family of MET exon 14 skipping mutations (METex14) identified in NSCLC join the growing list of approved targeted therapeutics. In contrast to other actionable drivers, METex14 is frequently detected in smokers and is known to occur in squamous NSCLC. We aimed to explore the heterogeneous mutational landscape within METex14 NSCLC by specific mutation, histology, and smoking status.

METHODS

NSCLC tissue samples were analyzed with DNA-based next-generation sequencing (NGS; 592 genes, NextSeq) or whole-exome sequencing (NovaSeq), RNA-based whole transcriptome sequencing (WTS, NovaSeq), and immunohistochemistry (IHC) at Caris Life Sciences (Phoenix, AZ). PD-L1 expression utilized the 22C3 clone (Dako); TMB-high was defined as ≥ 10 mt/Mb. Wilcoxon or Fisher's exact were used to determine statistical significance (p without and q with multi-comparison correction). Immune cell fraction (QuanTiseq) and pathway analysis (ssGSEA) were informed by WTS analysis.

RESULTS

In a cohort of 18,168 NSCLC tissue samples, 440 unique METex14 mutations were identified. One hundred forty-seven distinct mutations with more than 11 protein alterations were detected. D1028H (8.4%), D1028N (7.0%), c.3082+2T>C (5.7%), D1028Y (5.2%), and c.3082+1G>A (4.5%) were the most prevalent METex14 mutations. Overall, 8.6% were TMB-high. PD-L1 $\geq 1\%$ was present in 82.2% of METex14 patients but varied by mutation type, with a median PD-L1 tumor proportion score (TPS) of 97.5% in c.3082+1G>C and 0% in c.3082+3A>G ($q < 0.05$). Forty-nine cases had (11.1%) squamous histology, 381 (86.6%) had non-squamous histology, and 10 (0.2%) had adenosquamous histology. In squamous METex14-wild-type cases, 90.4% had TP53 mt ($p < 0.001$), 17.9% had KMT2D mt ($p < 0.05$), and 0.89% had POT1 mt ($p < 0.05$) compared to non-squamous, where 60.7% had TP53 mt, 2.7% had KMT2D mt, and 1.53% had POT1 mt. In squamous METex14-mt cases, 17.02% had TP53 mt ($p < 0.001$), 4.4% had KMT2D mt ($p < 0.05$), and 12.5% had POT1 mt ($p < 0.05$) compared to non-squamous, where 48.2% had TP53 mt, 0% had KMT2D mt, and 4.4% had POT1 mt. Squamous METex14 NSCLC had numerically shorter survival compared to non-squamous (HR 1.22, $p = 0.47$, mOS 336 vs. 1106 days). Smoking status was available for 93 METex14 cases. Seventy-nine cases (84.9%) had a history of smoking, and only 14 (15.1%) were nonsmokers, where 8 (8.6%) had squamous histology compared to 85 (91.4%) with non-squamous histology. Seventy-four (93.7%) cases with non-squamous histology had a smoking history, and three (21.4%) patients with squamous histology were lifelong nonsmokers. Those with a history of smoking were enriched in D1028H/Y and c.3082+2T>C subtypes. HLA-G mRNA expression is lower in those with a smoking history than in nonsmokers. Upregulation of the Epithelial-Mesenchymal Transition pathway is common in nonsmokers with METex14 NSCLC.

CONCLUSION

There is significant heterogeneity within METex14 NSCLC, with differences in co-mutations, TMB, and PD-L1 expression noted among different METex14 mutations. While METex14 is detected in both squamous and non-squamous NSCLC, there are differences in the enrichment of oncogenic pathways, which may explain the heterogeneity in response to various treatments. Future studies investigating specific METex14 alterations may allow more granular personalization of treatment for patients with METex14 NSCLC.

P03: Lung Cancer Approved Tyrosine Kinase Inhibitors that Inhibit MATE-1 can Lead to “False” Decreases in Renal Function

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BACKGROUND

Many tyrosine kinase inhibitors (TKIs) approved for the treatment of oncogene-driven lung cancers (e.g., brigatinib, lorlatinib, entrectinib, selpercatinib, prasletinib, capmatinib, and tepotinib) inhibit MATE-1. The fact that MATE-1 inhibition (MATEi) can increase serum creatinine in the absence of true kidney damage is not well recognized. A systematic analysis of MATEi-treated patients was conducted to evaluate the frequency of this side-effect.

METHODS

Data from patients with advanced solid tumors who received treatment with a MATEi TKI approved for lung cancer treatment (brigatinib, capmatinib, entrectinib, lorlatinib, pralsetinib, selpercatinib, or tepotinib) were reviewed for evidence of renal dysfunction on therapy. Acute kidney injury (AKI) was classified based on creatinine levels (KDIGO criteria) as stage 1 (>1.5x but <2x baseline), stage 2 (>2x but <3x baseline), or stage 3 (>3x baseline). Data on cystatin C, a marker of kidney function unaffected by MATEi, were compared.

RESULTS

We identified 387 patients. The TKIs administered were lorlatinib (25%, n=98), selpercatinib (24%, n=97), capmatinib (18%, n=71), entrectinib (17%, n=64), tepotinib (9%, n=34), brigatinib (5%, n=20), and pralsetinib (2%, n=6). Of the 52 patients with AKI, KDIGO stage 1, 2, and 3 was observed in 67% (n=35), 25% (n=13) and 8% (n=4) of patients, respectively. Concurrently drawn creatinine and cystatin C levels on TKI therapy were available for 21% (n=11/54) of patients. In almost all cases (91%, n=10/11), cystatin C was lower than creatinine, indicating that creatinine levels alone had underestimated true renal function. The glomerular filtration rate (GFR) in the ten patients was correspondingly improved in calculations based on cystatin C rather than creatinine. In a selpercatinib-treated patient with eighteen serial concurrent creatinine and cystatin C measurements over three years, cystatin C measurements uncovered improved GFR (relative to creatinine-calculated GFR) at most (95%, n=17/18) timepoints.

CONCLUSION

In the majority of cancer patients treated with TKIs that inhibit MATE-1, cystatin C corresponded to better renal function than creatinine. We recommend that providers consider concurrent cystatin C measurements in MATE-1 inhibitor-treated patients being evaluated for AKI, particularly if the level of kidney insufficiency prompts clinical action (e.g. dose reduction/discontinuation).

P04: Impact of STK11 and/or KEAP1 Deletion on Outcomes to Immunotherapy in Non-Small Cell Lung Cancer

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BACKGROUND

Mutations in the genes STK11 and KEAP1 are associated with worse responses to immune checkpoint inhibition (ICI) in NSCLC, particularly among patients with concurrent KRAS mutations. However, the impact of STK11 and KEAP1 gene deletions on ICI outcomes are not well characterized.

METHODS

Patients with non-squamous NSCLC at DFCI whose tumors underwent next-generation sequencing (NGS) were evaluated. Samples with low tumor purity (<20%) were excluded. Clinicopathologic variables and outcomes were analyzed according to KRAS status and STK11 or KEAP1 deletion.

RESULTS

Among 3194 patients with non-squamous NSCLC (median age 66, 61% women, 78% ever smokers, 59% stage IV), 578 (18%) had STK11 mutations, 500 (18%) had KEAP1 mutations, 471 (15%) had STK11 deletions (STK11DEL; 15 were bi-allelic deletions), and 374 (13.5%) had KEAP1 deletions (KEAP1DEL; 1 was bi-allelic). In non-STK11-mutant cases (of which 301 (11.5%) were STK11DEL) or non-KEAP1-mutant cases (of which 242 (10.6%) were KEAP1DEL) respectively, the frequency of STK11DEL or KEAP1DEL was generally higher in: men compared to women (STK11: $p=0.01$, KEAP1: $p=0.12$), in patients < 70 years compared to ≥ 70 years (STK11: $p=0.01$, KEAP1: $p=0.08$), and in ever-smokers compared to never-smokers (STK11: $p=0.08$, KEAP1: $p=0.05$). The frequency of STK11 deletion increased with increasing tumor stage ($p=0.02$). STK11 and KEAP1 deletion were associated with a lower median PD-L1 tumor proportion score (TPS) ($p<0.001$ for both), higher tumor mutational burden (TMB) (STK11: $p<0.001$, KEAP1: $p=0.01$), and higher aneuploidy by adjusted fraction of chromosomal arm alterations (FAA) ($p<0.001$ for both).

To probe the impact of STK11 and KEAP1 deletion on outcomes to ICI, we identified 717 patients with advanced non-squamous NSCLC who received ICI monotherapy. Among non-STK11-mutant cases treated with ICI, in KRASMUT NSCLC, STK11DEL was associated with a numerically lower overall response rate (ORR) (13.6% vs. 32.3%, $p=0.09$), a significantly shorter progression-free survival (PFS) (HR 1.8, $p=0.01$), and a numerically shorter OS (HR 1.5, $p=0.14$). There was no association between STK11DEL and ICI outcomes in KRASWT NSCLC. The association between STK11DEL and shorter PFS in KRASMUT NSCLC persisted in multivariate regression (accounting for age, sex, smoking, performance status, treatment line, KEAP1 mutation, PD-L1 TPS, TMB, and FAA.) Among non-KEAP1-mutant cases, in KRASMUT NSCLC, but not KRASWT NSCLC, KEAP1DEL was associated with a lower ORR (0% vs 31%, $p=0.004$), shorter PFS (HR 1.8, $p=0.03$), and shorter OS (HR 2.5, $p=0.001$) to immunotherapy. The association between KEAP1DEL and shorter OS (but not PFS) in KRASMUT tumors persisted in multivariate regression (accounting for age, gender, smoking, performance status, treatment line, STK11 mutation, PD-L1 TPS, TMB, and FAA). Comparing the impact of STK11 or KEAP1 mono-allelic deletion vs. mono-allelic mutation vs. "double hit" (bi-allelic deletion or mutation plus deletion) in KRASMUT cases, there was no difference in PFS or OS between these three groups.

CONCLUSION

STK11 and KEAP1 deletion may be linked to generally worse outcomes to ICI in KRASMUT NSCLC. Future analyses will explore this question in an independent cohort and assess the impact of these deletions on protein expression by immunohistochemistry.

P05: Genomic and Immunophenotypic Landscape of P05: Acquired Resistance (AR) to PD-(L)1 Blockade in Non-Small Cell Lung Cancer

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BACKGROUND

Although immune checkpoint inhibitors (ICI) have extended survival in patients with non-small cell lung cancer (NSCLC), acquired resistance (AR) to ICI often develops after an initial benefit. However, the mechanisms underlying AR to ICI in NSCLC are largely unknown.

METHODS

Tumor genomic profiling, machine learning-based assessment of tumor-infiltrating lymphocytes, multiplexed immunofluorescence (CD8/PD1/PD-L1/Foxp3/CK7), and HLA-I immunohistochemistry (IHC) were performed on matched pre- and post-ICI tumor biopsies from patients with NSCLC treated with ICI at Dana-Farber Cancer Institute who developed acquired resistance to ICI. Two control cohorts of patients with pre- and post-chemotherapy and targeted therapy tumor biopsies were also examined. AR to treatment was defined as disease progression after an objective response or stable disease ≥ 3 months.

RESULTS

Among 1823 ICI-treated patients with advanced NSCLC, 80 developed AR and had matched pre- and post-ICI samples. Resistance mutations were identified in 27.3% of cases (Figure 1A). The most common included acquired loss-of-function mutations in STK11 (9.1%), B2M (6.5%), NF1/2 (5.2%), SMARCA4 (5.2%), APC (3.9%), KEAP1 (2.6%), and JAK1 (2.6%). Acquired activating mutations were found in PI3KCA (3.9%) and SOS1 (1.3%). We also identified acquired copy number variations in 49.3% of cases, including heterozygous loss of B2M (23.4%), STK11 (16.8%), SMARCA4 (16.9%), KEAP1 (15.6%), PTEN (10.4%), CDKN2A/B (9.1%) and CD274/PDCD1LG2 (encoding PD-L1 and PD-L2, respectively) (9.1%). We also noted acquired homozygous deletions in CDKN2A/B (9.1%), CD274/PDCD1LG2 (1.3%), and JAK1 (1.3%), as well as acquired amplification in MDM2 (5.2%) and MYC (2.6%). Machine learning analysis of 16 cases with pre- and post-ICI digitalized histologic images showed a decrease in intratumoral lymphocytes at the time of resistance (88 vs 36 cells/mm², $P=0.03$, Figure 1B). Among 6 patients with pre- and post-ICI multiplexed immunofluorescence we observed a decrease in CD8+/PD1+ T-cells in ICI-resistant samples (24 vs 10 cells/mm², $P=0.01$, Figure 1C-D). Among 7 patients with available HLA-I IHC, we found a decrease in HLA-I expression by H-score at the time of resistance (300 vs 260, $P=0.03$, Figure 1E-F). In control cohorts of patients who received chemotherapy (N=30) or targeted therapies (N=89), no acquired mutations in STK11, KEAP1, B2M, JAK1, APC, and SOS1 were detected. Intervening chemotherapy and targeted therapies were not associated with changes in lymphocyte infiltration or HLA-I expression at the time of resistance.

CONCLUSION

Mechanisms of AR to ICI are heterogenous, including genomic and immunophenotypic factors. New therapeutic strategies to overcome ICI resistance may need to be individualized for patients with NSCLC depending on the resistance mechanism.

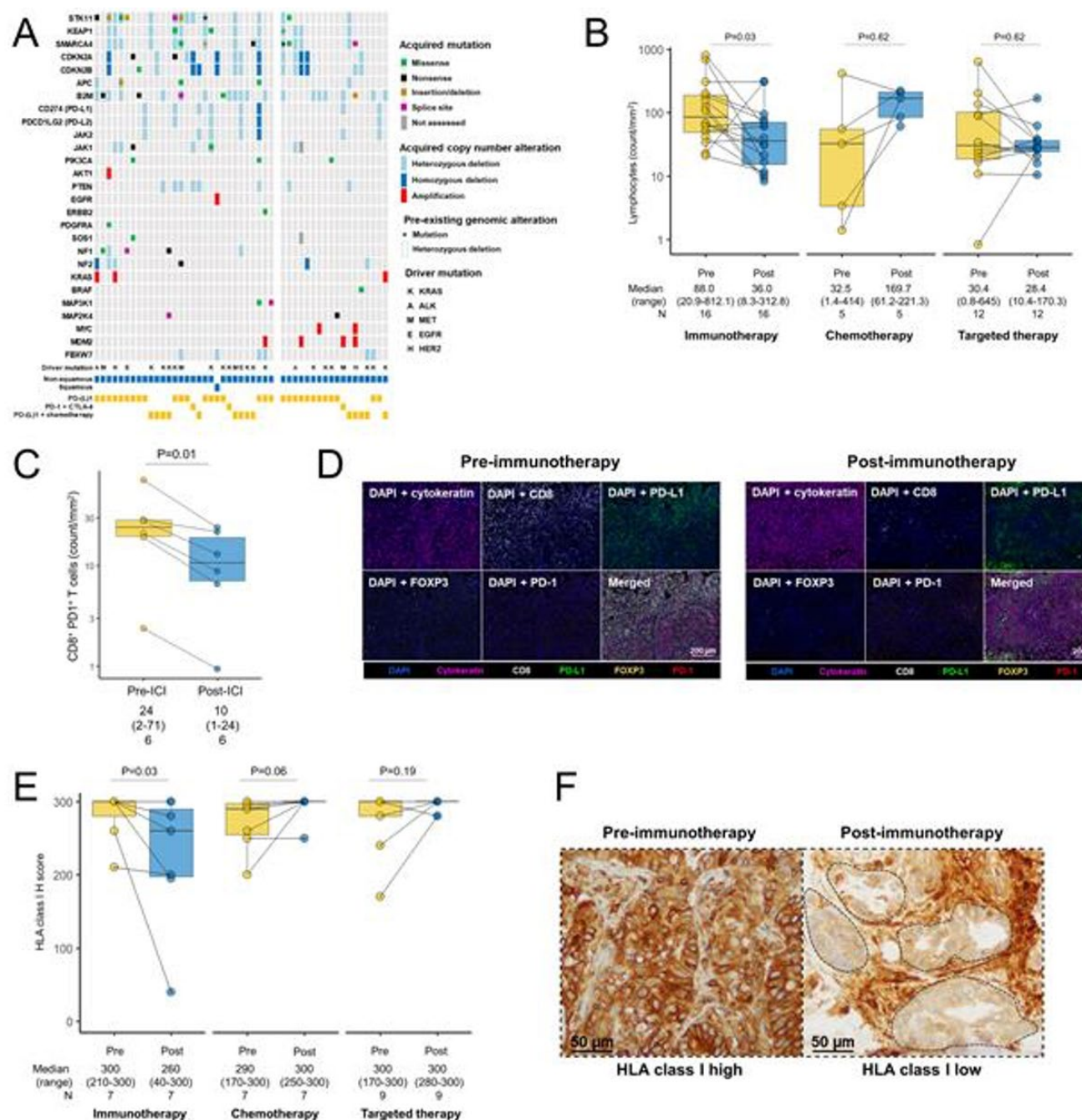


Figure 1. (A) Summary of the genomic changes identified at the time of acquired resistance to PD-(L)1 based therapies in patients with NSCLC. Only genomic alterations in the post-ICI biopsy that were not present in the pre-ICI biopsy are displayed. (B) Paired box-plots showing the change in the density of tumor-infiltrating lymphocytes among patients with pre- and post-treatment standard H&E slides which underwent immune cell density assessment using machine learning. (C) Paired box-plots showing changes in CD8+PD1+ T-cells in patients with pre- and post-immunotherapy tumor samples which underwent multiplexed immunofluorescence. (D) Representative case of a patient with (left) pre- and (right) post-immunotherapy multiplexed immunofluorescence showing significant decrease in intratumoral CD8+ T-cells. (E) Paired box-plots showing absolute changes in HLA class I H-score among patients with pre- and post-immunotherapy, chemotherapy and targeted therapy samples which underwent HLA class I immunohistochemistry. (F) Representative case of pre- and post-immunotherapy tumor biopsy showing significant decrease in HLA class I expression at the time of acquired resistance. * ICI, Immune checkpoint inhibitor.

P06: Real World Outcomes of Lurbinectedin as Second Line Treatment in Extensive Stage-Small Cell Lung Cancer (ES-SCLC)

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BACKGROUND

Patients with SCLC have limited therapeutic options after chemoimmunotherapy. Lurbinectedin, an alkylating agent, has received accelerated approval by the US Food and Drug Administration (FDA) for patients with metastatic SCLC progressing on standard frontline therapies. Here, we describe our institutional experience using lurbinectedin in second line setting for ES-SCLC.

METHODS

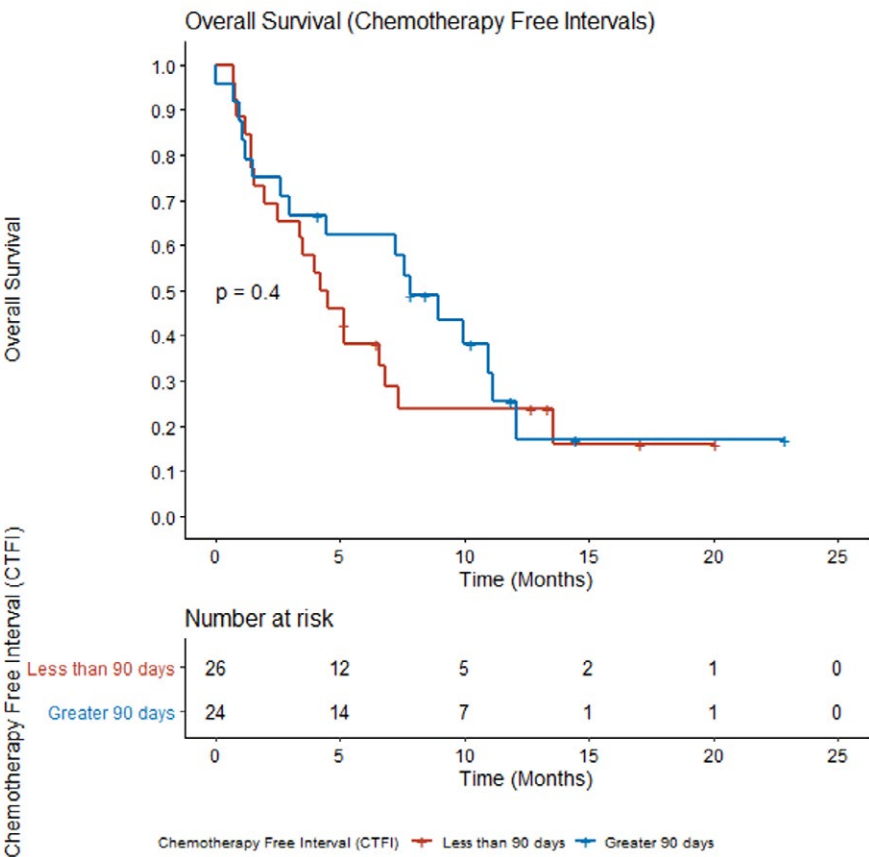
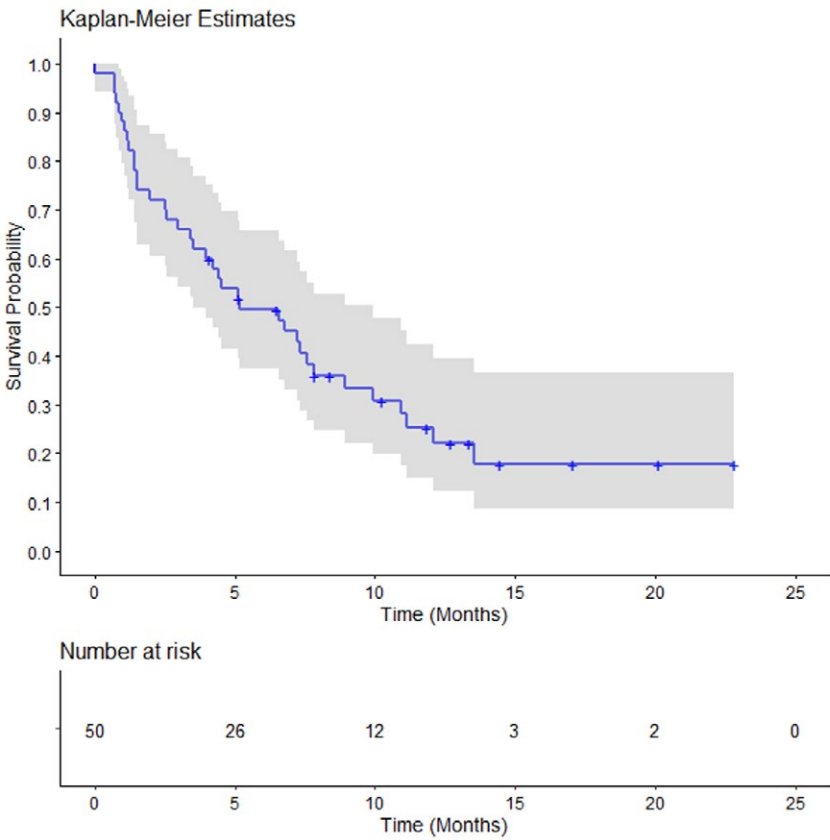
We identified 90 unique patients who received lurbinectedin between June 2020 to June 2022 for SCLC at our institution. We excluded patients who received lurbinectedin in the third-line or beyond, extrapulmonary small cell cancers, and poorly differentiated neuroendocrine cancers. Fifty patients met our criteria and data on the following variables were extracted for each: age at diagnosis, sex, receipt of prior platinum chemotherapy and/or immunotherapy, number of cycles, date of lurbinectedin initiation, dose, date of progression, date of last followup, chemotherapy-free interval (CTFI), and toxicities.

RESULTS

Within the cohort, median age at diagnosis was 67 years, with 50% females. The median follow-up from diagnosis and initiation of treatment was 13.3 and 5 months respectively. Of these, 94% (47/50) had de novo SCLC, while 6% (3/50) had SCLC transformed from NSCLC. Eighty-two percent of patients had ES-SCLC at diagnosis. Median number of cycles of lurbinectedin was 3 (range: 1-25) with most receiving standard dose of 3.2 mg/m² (76%). Twelve patients (24%) patients received empiric dose reduction due to history of myelosuppression with previous chemotherapy, fatigue, or frailty. The median CTFI among the cohort was 74 days with 52% (26/50) CTFI <90, 40% (20/50) CTFI 90-180, and 8% (4/50) CTFI > 180 days. Grade 3 or higher adverse events reported were neutropenia (12%), anemia, thrombocytopenia, and elevated ALT (6% each). Twelve percent of patients required dose reduction due to myelosuppression (neutropenia, thrombocytopenia) or fatigue. Growth factor support given in 20% of patients either as secondary prophylaxis for neutropenia (14%) or as primary prophylaxis (6%). There were no grade 5 toxicities with lurbinectedin at 3.2 mg/m². Overall, the median progression free survival (PFS) for the cohort was 2.08 months, with a median overall survival (OS) of the cohort of 5.1 months. There was numerical but not statistically significant improvement in OS for patients with longer CTFI before initiation of lurbinectedin.

CONCLUSION

Lurbinectedin was generally well tolerated in relapsed/refractory SCLC. However, real world outcomes in patients with SCLC are suboptimal, highlighting the urgent need for improved strategies for patients with SCLC.



Characteristics	Results (n=50)
No. of cycles of therapy (median, range)	3 (range: 1-25)
Dose Administered	
3.2 mg/m ² (number, %)	38 (76%)
Other (number, %)	12 (24%)
Dose Reduction	
Empiric (number, %)	12 (24%)
Due to adverse events (number, %)	6 (12%)
Adverse Events (Grade ≥3)	
Neutropenia (number, %)	6 (12%)
Anemia (number, %)	3 (6%)
Fatigue (number, %)	3 (6%)
Febrile Neutropenia (number, %)	3 (6%)

P07: Co-occurring Alterations in Multiple Tumor Suppressor Genes are Associated with Worse Outcomes in Patients with EGFR-Mutant Lung Cancer

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BACKGROUND

Tumors from patients with EGFR-mutant NSCLC inevitably recur under tyrosine kinase inhibitor (TKI) therapy. Co-occurring alterations in tumor suppressor genes (TSG) beyond TP53 have been associated with disease heterogeneity, however, detailed analyses of their impact on patient outcome are lacking.

METHODS:

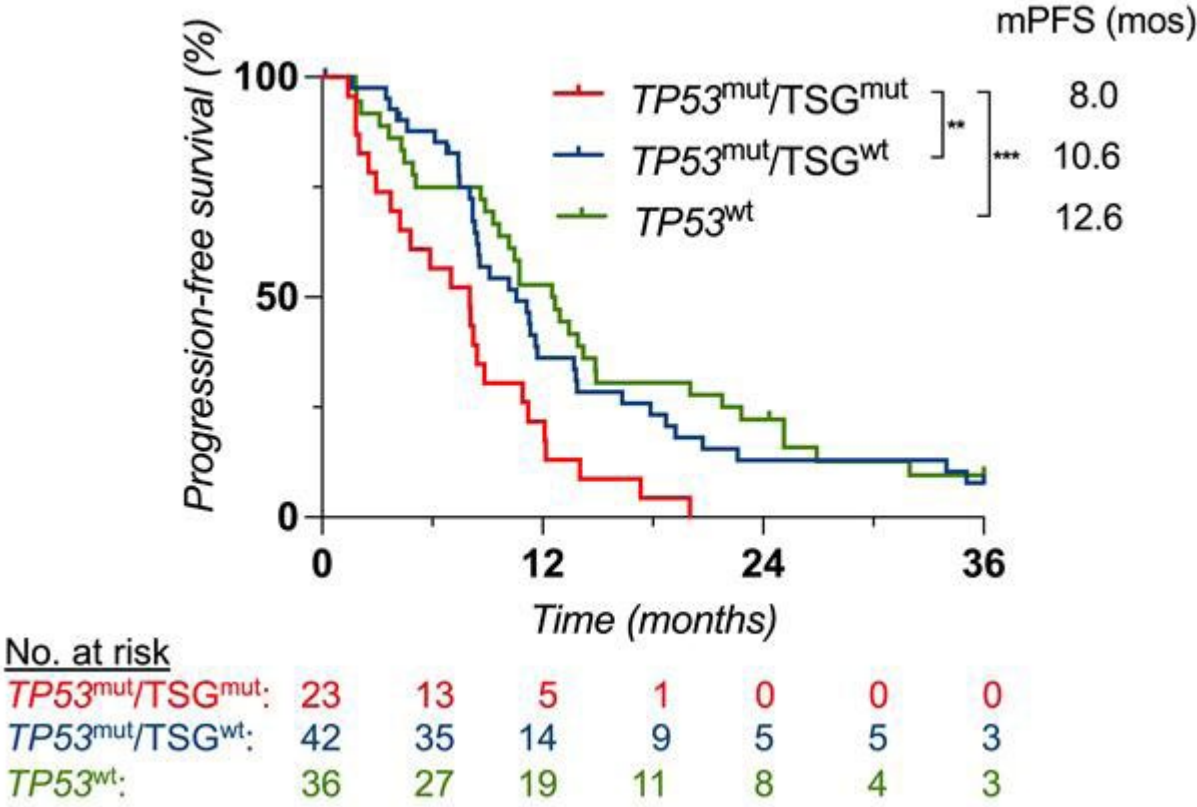
Patients with EGFR-mutant NSCLC treated with EGFR-TKIs at the Yale Cancer Center who had tumor genomic profiling were included. Alterations in TP53 and five additional TSGs (RB1, NF1, ARID1A, BRCA1 and PTEN), which were more commonly mutated in TP53mut than TP53wt tumors, were used to stratify the cohort into the following subgroups: patients with tumors harboring a TP53 mutation plus a mutation in at least 1 additional TSG (TP53mut/TSGmut), patients with tumors harboring a TP53 mutation without an additional TSG mutation (TP53mut/TSGwt), and patients with TP53 wild-type tumors (TP53wt). Clinical characteristics including progression-free (PFS) and overall survival (OS) were assessed in those subgroups, and similar analyses were performed in a separate patient cohort included in the AACR Project GENIE database.

RESULTS:

One-hundred-one patients with EGFR-mutant NSCLC were retrospectively included. TP53 mutations were identified in 65 (64%) tumors, of which 23 (35%) and 42 (65%) were classified as TP53mut/TSGmut and TP53mut/TSGwt, respectively. Among all included patients, the presence of a TP53 mutation weakly associated with worse PFS (HR 1.46, $p=0.09$) and OS (HR 1.68, $p=0.04$). Strikingly, after stratifying the TP53mut cohort into TP53mut/TSGmut and TP53mut/TSGwt cases, we identified that additional TSG alterations were driving the poor outcomes: patients with TP53mut/TSGmut tumors had significantly worse PFS (Figure 1) and OS on EGFR-TKI than TP53mut/TSGwt (mPFS 8.0 vs 10.6 months, $p=0.006$; mOS 30.0 vs 33.3 months, $p=0.12$) or TP53wt cases (mPFS 8.0 vs 12.6 months, $p<0.0001$; mOS 30.0 vs 48.8 months, $p=0.001$). There were no significant outcome differences between patients with TP53mut/TSGwt and TP53wt tumors. To validate our findings in an independent cohort of patients with EGFR-mutant NSCLC, we interrogated the GENIE database. Similar to the Yale cohort, in the GENIE cohort ($n=182$) patients with TP53mut/TSGmut tumors had significantly worse PFS compared to patients with TP53mut/TSGwt (mPFS 2.5 vs 7.7 months, $p=0.001$) or TP53wt tumors (mPFS 2.5 vs 9.6 months, $p<0.001$). Similar outcome differences were seen between the groups for OS.

CONCLUSION:

The inferior outcomes in patients with EGFR-mutant NSCLC with tumors harboring a co-occurring TP53 mutation may be due to additional TSG alterations rather than TP53 mutational status alone. This may have implications for understanding the biologic underpinnings of differential outcomes to EGFR-TKIs.



P08: Pivotal Data Update from the Phase 1/2 TRIDENT-1 Trial of Repotrectinib in Patients with ROS1+ Advanced Non-Small Cell Lung Cancer (NSCLC)

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BACKGROUND

Repotrectinib is a next-generation ROS1 and TRK tyrosine kinase inhibitor (TKI) under evaluation in the global pivotal phase 1/2 TRIDENT-1 trial (NCT03093116). We report results in TKI-naïve and TKI-pretreated patients with advanced, ROS1 fusion-positive (ROS1+) NSCLC.

METHODS

Patients with ROS1+ NSCLC were assigned to 1 of 4 expansion cohorts. The phase 2 primary endpoint was confirmed objective response rate (cORR) by blinded independent central review (BICR). Secondary endpoints included duration of response (DOR), clinical benefit rate (CBR), progression-free survival (PFS), overall survival, intracranial ORR (icORR), cORR in TKI-pretreated patients with ROS1 G2032R NSCLC, safety, and patient-reported outcomes. Efficacy included pooled data from phase 1 (40 mg QD to 160 mg QD and 160 mg BID) and phase 2 (recommended phase 2 dose of 160 mg QD x 14 days followed by 160 mg BID); the safety analysis included all patients who received ≥1 dose of repotrectinib.

RESULTS

As of June 20, 2022, the primary efficacy population included 71 TKI-naïve patients and 56 TKI-pretreated patients with 1 prior ROS1 TKI and no prior chemotherapy (chemo). In TKI-naïve patients, cORR (95% CI) was 79% (68, 88); 12-month DOR (95% CI) was 86% (76, 96); 12-month PFS (95% CI) was 80% (70, 90). Additional efficacy data, including outcomes in TKI-pretreated cohorts and cORR by age, are shown in the Table. In TKI-pretreated patients with ROS1 G2032R NSCLC (n = 17), cORR was 59% (6-month DOR [95% CI]: 70% [42, 98]). In the overall safety population (n = 444), any-grade treatment-emergent adverse events (TEAEs) reported in ≥20% of patients were dizziness (61%), dysgeusia (49%), constipation (37%), anemia (35%), paresthesia (32%), dyspnea (29%), fatigue (24%), nausea (21%), and alanine transaminase increase (21%). Dose reductions and drug discontinuation were required in 34.0% and 9.7% of patients, respectively. Among patients aged ≥18-<65 years (n = 329), ≥65-<75 years (n = 88), and ≥75 years (n = 27), incidence of grade ≥3 TEAEs was 48%, 59%, and 59%, respectively. Additional results of the safety analysis in key patient subgroups will be presented.

CONCLUSION

In both TKI-naïve and TKI-pretreated patients with ROS1+ advanced NSCLC, repotrectinib achieves durable activity, including intracranial responses, and responses in those with ROS1 G2032R. With a longer follow-up, repotrectinib remains well tolerated with a manageable safety profile. Efficacy and safety were generally consistent across age subgroups.

TRIDENT-1: Repotrectinib in ROS1+ advanced NSCLC

	ROS1 TKI-naïve (n = 71)	1 prior ROS1 TKI + no prior chemo (n = 56)	1 prior ROS1 TKI + 1 platinum- based chemo (n = 26)	2 prior ROS1 TKIs + no prior chemo (n = 18)
cORR, ^a % (95% CI)	79 (68, 88)	38 (25, 52)	42 (23, 63)	28 (10, 54)
CBR, % (95% CI)	94 (86, 98)	82 (70, 91)	73 (52, 88)	44 (22, 69)
DOR at 6 months, ^b % (95% CI)	91 (83,99)	80 (62, 98)	64 (35, 92)	60 (17, 100)
PFS at 6 months, ^b % (95% CI)	91 (84,98)	67 (54, 81)	39 (19, 58)	22 (3, 41)
icORR, ^{c,d} % (95% CI) Evaluable, n	88 (47, 100) 8	42 (15, 72) 12	50 (7, 93) 6	
cORR, ^a % (95% CI) by age	ROS1 TKI-naïve (n = 71)	ROS1 TKI pretreated (n = 100)		
Aged ≥18-<65 (n)	81 (68, 90) (52)	38 (27, 50) (79)		
Aged ≥65-<75 (n)	67 (38, 88) (15)	31 (11, 59) (16)		
Aged ≥75 (n)	100 (0, 60) (4)	40 (5, 85) (5)		
^a By BICR per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. ^b Assessed by Kaplan-Meier estimates. ^c In patients with measurable central nervous system metastases at baseline. ^d icORR assessed by modified RECIST v1.1 in evaluable patients in the phase 2 portion of study.				

P09: Activating MET Kinase Domain Mutations Define a Novel Targetable Molecular Subtype of Non-Small Cell Lung Cancer that is Clinically Sensitive to MET Inhibitor Elzovantinib (TPX-0022)

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BACKGROUND

In non-small cell lung cancer (NSCLC), MET exon 14 skipping mutations (METex14mut) and MET amplification can be effectively targeted with MET inhibitors. Here, we define a novel, potentially targetable molecular subtype of NSCLC harboring activating MET TKD mutations (MET-TKDmut) without concurrent METex14mut.

METHODS

Clinicopathologic and genomic data were abstracted from non-overlapping cohorts of NSCLCs that underwent genomic profiling in the GENIE v11.1, China PanCancer (Origimed, Nature 2022), The Cancer Genome Atlas (TCGA), Dana-Farber Cancer Institute (DFCI), and Memorial Sloan Kettering Cancer Center (MSKCC) datasets (multi-institutional cohort). An independent cohort of NSCLC tissue and liquid samples from the Foundation Medicine (FMI) genomic database was also examined. MET-TKDmut were defined as “oncogenic” or “likely oncogenic” according to OncoKB annotation.

RESULTS

A total of 23,195 patients with NSCLC in the multi-institutional cohort and 92,406 patients with NSCLC in the FMI cohort were analyzed: 44 (0.2%) and 129 (0.14%) patients in the multi-institutional and FMI cohorts, respectively, had a tumor harboring an oncogenic / likely oncogenic MET-TKDmut without concurrent METex14mut, including (ordered from high to low prevalence): H1094Y/D/L/N/R, D1228N/H/G/V/Y, Y1230H/C/N, L1195V/F, V1220L/I, M1250T/I, F1200I/L/V, N1100S/T, H1106D/Y, F1080L/S/V, V1188I, and Y1235H. Comprehensive clinicopathological data were available for 29 patients from DFCI and MSKCC with NSCLC harboring oncogenic / likely oncogenic MET-TKDmut without concurrent METex14mut: median age was 60 years old (range: 30-88), 18 (62%) were female, 19 (66%) were white, 16 (55%) had a history of tobacco use with a median pack-years of 25 [range: 5-80], 26 (90%) had lung adenocarcinoma, and 23 (82%) had a stage IV disease at the time of MET TKD mutation detection. PD-L1 tumor proportion score, available for 19 tumors, was < 1% in 5 (26%), 1-49% in 7 (37%) and ≥ 50% in 7 (37%) cases. Among these 29 cases, 13 showed MET-TKDmut as a de-novo genomic event in NSCLC: in 7 cases were detected in the absence of other driver mutations; 2 cases harbored a MET-TKDmut with concurrent MET amplification; 4 cases showed a MET-TKDmut along with a concurrent KRAS driver mutation. In the remaining 16 cases, MET-TKDmut were detected as putative mechanisms of resistance to kinase inhibitors directed against other (non-METex14mut) driver mutations. Confirmed partial responses to the MET inhibitor elzovantinib (TPX-0022) were achieved in two patients with MET TKD-mutant NSCLC and no other concurrent driver mutations: a 64-year-old man with MET H1094Y-mutant lung adenocarcinoma, and an 80-year-old man with MET F1200I-mutant lung adenocarcinoma. The patient with H1094Y-mutant lung adenocarcinoma, after 21 months of treatment with elzovantinib, progressed and genomic profile on tumor tissue re-biopsy showed acquired EGFR amplification as potential mechanism of resistance.

CONCLUSION

Activating MET TKD mutations without concurrent MET exon 14 mutations were detected in ~ 0.2% of NSCLC, and occur in the absence of other known drivers in a subset of cases. Comprehensive genomic profiling to detect these alterations and guide treatment selection and clinical trial enrollment is warranted.

P10: Impact of Aneuploidy and Chromosome 9p Loss on Tumor Immune Microenvironment and Immune Checkpoint Inhibitor Efficacy in Non-Small Cell Lung Cancer

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BACKGROUND

Although focal copy number alterations have been studied as a potential biomarker of immunotherapy efficacy in non-small cell lung cancer (NSCLC), the impact of aneuploidy burden and chromosomal arm-level events on immune checkpoint inhibitor (ICI) efficacy in NSCLC is uncertain.

METHODS

Patients who received ICI at two academic centers were included. Among nonsquamous NSCLCs which underwent targeted next-generation sequencing, we retrospectively quantified aneuploidy using the adjusted fraction of chromosomal arm alterations (FAA), defined as the number of altered chromosome arms divided by the number of chromosome arms assessed, adjusted for tumor purity. Multiplex immunofluorescence to quantify CD8, FOXP3, PD-1, and PD-L1 expression was performed on a separate cohort of nonsquamous NSCLCs to determine differences in tumor immune cells subsets according to FAA levels and arm-level events of interest.

RESULTS

Among 2293 nonsquamous NSCLCs identified, the median FAA (mFAA) increased with more advanced cancer stage (stage I: 0.04, stage II: 0.06, stage III: 0.07, stage IV: 0.08, $P < 0.001$) and decreased with higher PD-L1 tumor proportion score (TPS) levels (mFAA in TPS <1%: 0.09, TPS 1-49%: 0.08, TPS ≥50%: 0.05, $P < 0.001$). There was a very weak correlation between FAA and tumor mutational burden when taken as continuous variables (R : 0.07, $P < 0.001$). When assessed by site of biopsy, lesions from liver and brain had the highest FAA (median [range] 0.11 [0-0.43] and 0.10 [0-0.35], respectively), while tumor samples from lung and pleura had the lowest FAA (median [range] 0.05 [0-0.57] and 0.08 [0-0.40], respectively). By oncogenic driver status, NSCLCs with RET rearrangements and EGFR mutations and those with no known driver mutation tended to have a higher FAA, while those with BRAF, MET, and KRAS mutations had a lower FAA.

A total of 765 advanced nonsquamous NSCLCs with available FAA values were treated with ICIs. With decreasing FAA tertiles, there was a progressive improvement in objective response rate (ORR 15.1% in upper tertile vs 23.2% in middle tertile vs 28.4% in lowest tertile, $P < 0.001$), median progression-free survival (mPFS 2.5 vs 3.3 vs 4.1 months, $P < 0.001$), and median overall survival (mOS 12.5 vs 13.9 vs 16.4 months, $P = 0.006$), respectively. In the arm-level enrichment analysis, chromosome 9p loss was significantly enriched in ICI non-responders after false discovery rate adjustment. Compared to NSCLCs without chromosome 9p loss ($N = 452$), those with 9p loss ($N = 154$), had a lower ORR (28.1% vs 7.8%, $P < 0.001$), a shorter mPFS (4.1 vs 2.3 months, $P < 0.001$), and a shorter mOS (18.0 vs 9.6 months, $P < 0.001$) to immunotherapy. Chromosome 9p loss in tumors with PD-L1 TPS ≥50% resulted in a significantly lower ORR (6% vs 43%, $P < 0.001$), a significantly shorter mPFS (2.6 vs 6.4 months, HR: 1.94; $P < 0.001$), and a significantly shorter mOS (14.3 vs 30.2 months, HR: 1.98; $P < 0.001$) compared with NSCLCs with intact 9p arm and a high PD-L1 expression. Multiplexed

immunofluorescence demonstrated that tumors with either high FAA levels or chromosome 9p loss had significantly fewer tumor-associated immune cells.

CONCLUSION

NSCLCs with high aneuploidy and chromosome 9p loss have a distinct tumor immune microenvironment and less favorable outcomes to ICIs.

P11: A Phase 1 Trial of BI 1810631, a HER2 Tyrosine Kinase Inhibitor (TKI), as Monotherapy in Patients with Advanced/Metastatic Solid Tumors with HER2 Aberrations

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BACKGROUND

There is an unmet need for effective tyrosine kinase inhibitors (TKIs) against mutated HER2 in solid tumors, particularly in non-small cell lung cancer (NSCLC). BI 1810631 is a HER2-selective TKI that covalently binds to both wild-type and mutated HER2 receptors, including exon 20 insertions, while sparing EGFR signaling; preclinical data suggest good tolerability and efficacy. This phase 1a/1b, open-label, non-randomized study aims to determine the safety, maximum tolerated dose (MTD), pharmacokinetics (PK), pharmacodynamics and preliminary efficacy of BI 1810631 in patients with HER2 aberration-positive solid tumors (NCT04886804). Here we present results of phase 1a.

METHODS

In phase 1a, patients with HER2 aberration-positive (overexpression, gene amplification, somatic mutation, or gene rearrangements) advanced/unresectable/metastatic solid tumors refractory/unsuitable for standard therapy were enrolled. Patients received escalating doses of BI 1810631 BID (starting dose: 15 mg) or BI 1810631 QD (starting dose: 60 mg). Phase 1b will initially include 30 patients with advanced HER2 tyrosine kinase domain mutation-positive, pre-treated NSCLC. Additional cohorts may be included in the future. Primary endpoints: MTD based on number of dose-limiting toxicities (DLTs); number of patients with DLTs (phase 1a); objective response (phase 1b). Secondary endpoints: number of patients with DLTs throughout the entire treatment period and PK parameters (phase 1a/1b); duration of response, disease control, duration of disease control and progression-free survival (phase 1b).

RESULTS

As of October 18, 2022, 29 patients have been treated in the United States, the Netherlands, Japan, and China. Patients had NSCLC (n=18), colorectal cancer (n=3), other tumors (n=8). Most patients had a pathological HER2 mutation (n=20). Patients received BI 1810631 in either a BID (n=17) or a QD (n=12) schedule. Median number of cycles was 4 (range 1-12). Treatment is ongoing in 16 patients. To date, 1 DLT has been observed (grade 2 edema in the 60 mg BID cohort). The MTD has not been reached with either schedule. Treatment-related adverse events (TRAEs) have been reported in 17 patients (59%). The most common TRAEs were diarrhea (n=8), increased alkaline phosphatase (ALP) (n=2), anemia (n=2), increased creatinine (n=2), hypocalcemia (n=2), and hypoalbuminemia (n=2). There were 2 grade ≥ 3 TRAEs: anemia (n=1) and increased alanine transaminase (ALT) (n=1). In 23 patients evaluable for response the overall response rate (ORR) was 39% (n=9; NSCLC: n=7; esophagus, cholangiocarcinoma: n=1). The disease control rate (DCR) was 83%. In 14 patients with NSCLC with HER2 mutation evaluable for response, the ORR was 50% and the DCR was 93%.

CONCLUSION

These preliminary data indicate that BI 1810631 is well tolerated and shows encouraging anti-tumor activity in patients with HER2 aberration-positive solid tumors. Recruitment into phase 1a is ongoing.

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P12: Activity of Gilteritinib in Resistant ROS1 Rearranged Non-Small Cell Lung Cancer

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BACKGROUND

The incidence of ROS1 rearrangements in non-small cell lung cancer (NSCLC) ranges from 1-2%. ROS1-positive NSCLC patients are treated with FDA approved ROS1 tyrosine kinase inhibitors (TKI), crizotinib and entrectinib. Emergence of TKI resistance is a major hurdle limiting survival of patients. Kinase-intrinsic resistance mechanisms account for 10-50% of crizotinib-resistance in patients. ROS1 G2032R kinase domain mutation is responsible for majority of crizotinib and lorlatinib resistance; however emerging next-generation inhibitors repotrectinib, taletrectinib and NVL-520 are active against ROS1 G2032R. With implementation of ROS1 G2032R-combating TKI, ROS1 L2086F is emerging as a mutation highly resistant to most ROS1 TKI. Here, we investigated activity of type I and type II ROS1 TKI, entrectinib and cabozantinib, respectively as compared to the FLT3 inhibitor, gilteritinib against recurrent ROS1 kinase domain mutations, including L2086F. Gilteritinib was reported to inhibit several ALK resistant mutations but its activity in ROS1 resistance is currently unknown.

METHODS

Dose response cell viability and immunoblotting experiments to test activity of entrectinib, cabozantinib and taletrectinib were conducted in transformed Ba/F3 cells CD74-ROS1 and EZR-ROS1 fusions with wild type or mutant (F2004C, G2032R, L2086F) kinase domains. Non-linear regression curve fit analysis was used to determine 50% inhibitory concentration (IC₅₀). Phospho-specific antibodies were used to detect target (ROS1) and effector protein (ERK1/2) phosphorylation in lysates prepared from treated cells. We performed in vivo efficacy studies using subcutaneous flank allograft tumor model and oral gavage with TKI. The percent change in tumor volume in mice treated with taletrectinib or cabozantinib was compared with vehicle treatment.

RESULTS

IC₅₀ data summarized in the heatmap shows that ROS1 F2004C, ROS1 G2032R and ROS1 L2086F are entrectinib resistant. Cabozantinib, consistent with our previous published data harbors robust activity against ROS1 G2032R and ROS1 L2086F, however cabozantinib-resistance is imposed by ROS1 F2004C mutation. Gilteritinib, intriguingly, is active with IC₅₀ ≤ 25 nM against both ROS1 F2004C and ROS1 L2086F but not ROS1 G2032R. Dose response data are validated by correlative on-target inhibition of ROS1 auto-phosphorylation and effector ERK1/2 activation as seen in immunoblots and densitometry.

CONCLUSION

Gilteritinib is a viable clinical option in case of ROS1 L2086F resistance, which we predict, will become the prevalent resistance liability in the future. It is important to consider the adverse event profiles of cabozantinib, that to date is the only agent with activity against ROS1 L2086F, to gilteritinib's tolerability for consideration of best clinical agent in patients. This is especially a concern with compound mutations or subclonal populations harboring dual mutations that require combination treatment with both type I and type II ROS1 TKI. Gilteritinib is primarily used to treat FLT3-driven myeloid leukemia, and some preliminary conclusions can be drawn from these treated patients. Gilteritinib seems to have fewer overlapping toxicities with type I inhibitors like crizotinib or lorlatinib as compared to cabozantinib, and overall may have better tolerability owing to its lack of VEGFR inhibitory activity which limits cabozantinib's use in many patients. We recommend further investigation of gilteritinib in patients with ROS1 L2086F-driven TKI resistance who cannot tolerate cabozantinib at required effective dosing levels.

P13: MDM2 Inhibition in Combination with MEK Inhibition in Pre-Clinical Models of Lung Adenocarcinomas with MDM2 Amplification

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BACKGROUND

The eventual development of resistance to single-agent targeted therapies in lung adenocarcinomas (LUAD) is inevitable, and new strategies are needed. We hypothesize that combination therapies aimed at a known driver and a distinct targetable alteration could prolong time on oral targeted therapy.

METHODS

We mined the MSK-IMPACT large panel next-generation sequencing dataset for comutation patterns as candidates for combination therapy in LUAD. We investigated the small molecule MDM2 inhibitor milademetan in cell lines and patient-derived xenografts (PDXs) of lung adenocarcinoma with a known driver alteration and MDM2 amplification (MDM2amp). Several combination strategies were tested (milademetan in combination with MEK inhibition vs kinase or KRAS inhibition). Western blot analysis was used to evaluate protein activation and/or expression. Alterations in patient-derived models were confirmed by MSK-IMPACT testing.

RESULTS

In an analysis of 7636 patients with LUAD who underwent MSK-IMPACT sequencing, 5.5% (416/7636) harbored MDM2 amplification (MDM2amp), a known mechanism of TP53 inactivation. MDM2amp was over-represented among tumors with alterations in METex14 (34.4%, $p < 0.001$), EGFR (10%, $p < 0.001$), RET (11%, $p < 0.05$), and ALK (9.9%, $p < 0.002$). Milademetan caused growth inhibition as a single-agent in MDM2amp patient-derived cell lines with concurrent kinase alterations including ECLC5-GLx (MDM2amp/TRIM33::RET/TP53 wildtype (WT)) and LUAD12c (MDM2amp/METex14/KRASG12S/TP53 WT). Milademetan also caused growth inhibition in a cell line with KRASG12C and WT TP53 without MDM2amp (SW1573 (KRASG12C/TP53WT)), but not in cell lines with TP53 mutations (LUAD-002A1 (KIF5B::RET/TP53P128fs, H1792 (KRASG12C/TP53 splice site mut)). Treatment of ECLC5-GLx and LUAD12c with milademetan increased ERK phosphorylation, confirming a previous report of ERK activation upon MDM2 inhibition. This phenomenon was suppressed by concurrent milademetan and MEK inhibition using trametinib. In contrast, ERK phosphorylation was not suppressed by concurrent milademetan and KIF5B::RET inhibition using selpercatinib (in ECLC5-GLx), MET inhibition using capmatinib (in LUAD12c), or KRASG12C inhibition using sotorasib (in SW1573). The combination of milademetan+trametinib was synergistic in slowing growth of ECLC5-GLx, LUAD12c, and SW1573 cells, and increased expression of the pro-apoptotic proteins PUMA and BIM, beyond that achieved by either agent alone. In ECLC5-GLx, milademetan+trametinib also caused increased apoptosis as measured by Annexin-V compared to either agent alone (combination $p < 0.01$ compared to milademetan, $p < 0.001$ compared to trametinib). In vivo, milademetan+trametinib was more effective than milademetan or trametinib alone in ECLC5-GLx ($p < 0.0001$ and $p < 0.0001$, respectively), LX-285 (EGFRex19del/MDM2amp) ($p < 0.0001$ and $p < 0.0001$, respectively), L-13BS1 (model resistant to capmatinib) (METex14/MDM2amp) ($p < 0.05$ and $p < 0.0001$, respectively). In ECLC5-GLx cells treated with milademetan+trametinib, RNAseq analyses revealed reactivation of the TP53 pathway (as expected) and downregulation of cell cycle progression E2F pathways.

CONCLUSION

Combined MDM2/MEK inhibition is effective in patient-derived LUAD models harboring MDM2amp. This combination, potentially applicable to LUADs with a wide variety of oncogenic driver mutations and kinase fusions will be investigated as part of a phase 1/2 clinical trial.

P14: Differentiating Ensartinib from Lorlatinib and Alectinib for First Line Use in an ALK+ Non-Small Cell Lung Cancer Preclinical Model (ResCu)

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BACKGROUND

The objective of this study was to determine whether Ensartinib with its high potency and resistance suppressing properties creates a more favorable treatment profile when used as first-line therapy in ALK+ non-small cell lung cancer compared to two other ALK inhibitors, Alectinib and Lorlatinib.

METHODS

The ResCu system, a novel culturing system, allows for long term culture of cells without the need for passaging, allowing determination of treatment resistance that can develop over time in a physiologically relevant system that conserves the resistance pathways found in patients. Two ALK-dependent lung adenocarcinoma cell lines, H3122 and H2228 were used to derive starting populations for this study. Using ResCu, we drove resistance to three ALK inhibitors: alectinib, lorlatinib, and ensartinib by using a clinically equivalent dose.

A colony-forming-based assay of cells evolving in ResCu provided an indication of time to therapeutic resistance. The evolved cells were characterized for cross-sensitivity and resistance to a representative panel of 21 drugs. Cell viability was assessed by luminescence after 7 days of exposure to these secondary drugs.

RESULTS

The ResCu system developed resistant cell populations by evolutionary steering of H3122 and H2228 cell lines treated with ensartinib, alectinib, and lorlatinib. Genetic background had a significant effect on which ALKi exhibited the most durable response. The H2228 derived cell population became resistant to alectinib and lorlatinib by 14 days while ensartinib remained effective for at least 42 days. In contrast, H3122 derived cells became resistant to all ALK inhibitors tested by 14 days.

Rate of cross-resistance generation also varied between ALK inhibitors. Alectinib led to the highest levels of cross-resistance to other ALKi, approximately 3x higher. Lorlatinib led to highest levels of cross-resistance to other drug classes. Treatment with lorlatinib led to resistance in 13 other drug classes. Ensartinib led to least cross-resistance to ALKi and other drug classes. While the H3122 derived cells more rapidly evolved ALKi resistance, first line treatment with ensartinib sensitized them to lorlatinib, extending overall response to ALKi.

CONCLUSION

The ResCu system developed two ALKi resistant cell populations from distinct genetic backgrounds under physiologically relevant conditions. In one of the two genetic background ensartinib response was durable for greater than 42 days compared to 14 days with alectinib and lorlatinib. Alectinib led to the most cross-resistance to other ALKi while lorlatinib led to the most cross-resistance to other drug classes in both backgrounds. Biomarkers of ALKi escape and cross-resistance were derived from RNA-seq, and we are currently validating these alterations against clinical samples.

P15: Efficacy and Safety of Larotrectinib in Patients with Tropomyosin Receptor Kinase (TRK) Fusion Lung Cancer by Prior Line of Systemic Therapy and Performance Status

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BACKGROUND

Neurotrophic tyrosine receptor kinase (NTRK) gene fusions are oncogenic drivers in various tumors, including lung cancer. Larotrectinib is a highly selective, central nervous system (CNS)-active TRK inhibitor that demonstrated an objective response rate (ORR) of 73% across 15 investigator-assessed patients with lung cancer (Drilon et al. JCO Precis Oncol. 2022). We report data on patients with TRK fusion lung cancer treated with larotrectinib with longer follow-up.

METHODS

Patients with TRK fusion lung cancer enrolled in two larotrectinib clinical trials (NCT02576431 and NCT02122913) were included for this analysis. Larotrectinib was administered at 100 mg twice daily. Response was assessed by independent review committee (IRC) per RECIST v1.1. Patients were also stratified based on the number of prior systemic therapies and baseline Eastern Cooperative Oncology Group performance status (ECOG PS).

RESULTS

As of July 20, 2021, 26 patients with TRK fusion lung cancer had been enrolled, 12 of whom had known CNS metastases at baseline. Median age was 51.5 years (range 25.0–76.0). The gene fusions involved were NTRK1 (n=21) and NTRK3 (n=5). Patients received a median of two prior lines of systemic therapies. Among 23 patients evaluable per IRC, the ORR was 83% (95% confidence interval 61–95): two complete responses, 17 partial responses, and four stable disease (Table). Partial responses were observed in patients with ECOG PS of 2 or 3. Median time to response for all patients was 1.8 months. Median duration of response (DoR) and progression-free survival (PFS) were not reached; median follow-up was 12.9 and 14.6 months, respectively. The 24-month rates for DoR and PFS were 72% and 67%, respectively. The 24-month and 36-month overall survival (OS) rates were both 72%; median follow-up was 12.9 months. For the evaluable patients with CNS metastases, the 12-month DoR, PFS, and OS rates were 26%, 22%, and 78%, respectively. Duration of treatment for all patients evaluable ranged from 2.1 to 52.7+ months. By data cut-off, six of the patients that progressed continued treatment post-progression for ≥4 weeks. Treatment-related adverse events (TRAEs) were predominantly Grade 1–2. Grade 3 TRAEs occurred in five patients (increased alanine aminotransferase, increased aspartate aminotransferase, hypersensitivity, myalgia, and increased weight). No treatment discontinuations due to TRAEs occurred.

CONCLUSION

In this larger dataset with longer follow-up, larotrectinib demonstrated rapid and durable responses, extended survival, and a favorable long-term safety profile in patients with advanced lung cancer harboring NTRK gene fusions, including those with CNS metastases.

Table

	Number of prior lines of systemic therapy				Baseline ECOG PS				Patients with baseline CNS metastases	All patients (N=26)
	0	1	2	≥3	0	1	2	3		
Evaluable patients, n	1	6	6	10	8	12	1	2	10	23
ORR, % (95% CI)	100 (3–100)	83 (36–100)	83 (36–100)	80 (44–97)	100 (63–100)	67 (35–90)	100 (3–100)	100 (16–100)	80 (44–97)	83 (61–95)
Best overall response, n (%)										
CR	0	1 (17)	0	1 (10)	1 (13)	1 (8)	0	0	0	2 (9)
PR	1 (100)	4 (67)	5 (83)	7 (70)	7 (88)	7 (58)	1 (100)	2 (100)	8 (80)	17 (74)
SD	0	1 (17)	1 (17)	2 (20)	0	4 (33)	0	0	2 (20)	4 (17)

CI, confidence interval; CR, complete response; ORR, overall response rate; PR, partial response; SD, stable disease.

P16: Targetable Molecular Algorithm and Training Pathways Development for Treatment of the Non-Small Cell Lung Cancer

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BACKGROUND

Over the last decade, the treatment of patients with advanced non-small cell lung cancer (NSCLC) has become dependent on tissue and/or blood biomarkers to help guide treatment decisions. It is crucial to receive all the biomarker and tumor signature information in a single test with a fast turnaround time. While this ability was limited to simple mutations in the past, we are now seeing the rapid development of more complex biomarkers. In addition, biomarkers with matched therapies are relevant in a pan-cancer fashion.

Initial data from the MedStar Health system show considerable disparities in the use of next generation sequencing between hospitals. There is a clear need for creating protocols for making those decisions in an expeditious manner.

OBJECTIVES

Our aim was to increase the appropriate and timely use of NGS (Next Generation Sequencing) among health-system providers with the hope that this system will empower physicians to provide better care by providing a quick, simple, user-friendly tool for comprehensive patient care.

METHODS

The team developed separate algorithms for each identified targetable mutation in NSCLC (ex. EGFR). These algorithms were then developed into a clinical oncology training pathway website at Georgetown University Hospital. The website also contains references to appropriate trials, FDA drug inserts for the drugs and articles used to support the algorithm development. We rolled out the website along with a pre and post user survey. Target audience were Oncology, Internal medicine, and Pulmonology department at Medstar Georgetown and Washington Hospital Center.

RESULTS

Entry Survey was completed by 57 participants. 45 of them identified themselves as Physician in training, 6 identified as Oncology Physicians, 2 as Advanced practitioners and 4 as Others. On average the Physician in training group rated their pre-survey knowledge as 4/10 (on a scale of 1-10). Oncologists rated it as 9/10, APPs as 5/10 and Others as 5/10. Exit Survey was completed by 8 participants only. All the participants in exit survey said that they would recommend the TMA (Targetable Molecular Algorithm) algorithm to others for increasing their knowledge of NSCLC NGS. Most of them reported a 2-3-point increase in their NGS knowledge after using the website. On a scale of 1-10 with 10 being extremely easy to use, on an average the participants rated the ease of website/algorithm as 5/10.

CONCLUSION

Clinical pathways are systems-based tools for creating greater transparency around care decision making, therapeutic selection, care delivery, and they improve quality and efficiency by reducing non-value-added intra-provider variability in care. Increasing knowledge of Next generation sequencing for NSCLC to increase the utilization of targetable agents for patient's benefit is of utmost importance. As studies done have shown the survival benefit linked to those treatments when offered. While these preliminary data show good utility in NGS use and education that TMA can offer, we believe that including clinicians beyond the initial target audience can further our knowledge on key elements that impact adoption of NGS and understanding of the benefits.

P17: Clinical and Genomic Predictors of Response and Toxicity to Sotorasib in a Real-World Cohort of Patients with Advanced KRAS G12C-Mutant Non-Small Cell Lung Cancer

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BACKGROUND

With the recent approval of the KRAS G12C inhibitor sotorasib for patients with advanced KRAS G12C-mutant non-small cell lung cancer (NSCLC), there is a new need to explore efficacy and identify clinical and genomic factors associated with activity and toxicity among patients who are treated in routine clinical practice.

METHODS

We conducted a multicenter retrospective study of patients treated with sotorasib outside of the clinical trial setting to identify factors associated with real-world PFS (rwPFS) and clinically significant toxicity.

RESULTS

Among 93 patients with advanced KRAS G12C-mutant NSCLC treated with sotorasib, treatment led to a 26.7% real-world response rate, 5.0 month median rwPFS, and median time on treatment of 6.0 months. KEAP1 co-mutations were associated with shorter rwPFS (median 2.0 months vs 5.1 months in KEAP1-wild type patients; rwPFS hazard ratio [HR] 3.02, $p = 0.005$; Figure 1). No difference in rwPFS was observed among patients with and without TP53 co-mutations (HR 1.06, $p = 0.842$); STK11 co-mutations were associated with trends toward shorter rwPFS (HR 1.75, $p = 0.082$). All patients who developed grade 3 (G3) or higher treatment-related adverse events (TRAEs) had previously been treated with anti-PD(L)1 therapy, and anti-PD(L)1 therapy exposure within 12 weeks of sotorasib initiation was strongly associated with G3+ TRAEs ($p = 0.003$; Figure 2) and TRAE-related sotorasib discontinuation ($p = 0.022$). 23.9% of patients with recent anti-PD(L)1 therapy exposure developed G3+ TRAEs, and median rwPFS among patients with recent anti-PD(L)1 exposure was 2.9 months.

CONCLUSION

The activity of sotorasib in routine practice was modest in comparison to efficacy parameters reported in recent clinical trials, with KEAP1 co-mutations associated with clinical resistance and recent anti-PD(L)1 therapy exposure associated with toxicity. These observations may help further guide use of sotorasib in the clinic and may help inform the next generation of KRAS G12C-targeted clinical trials.

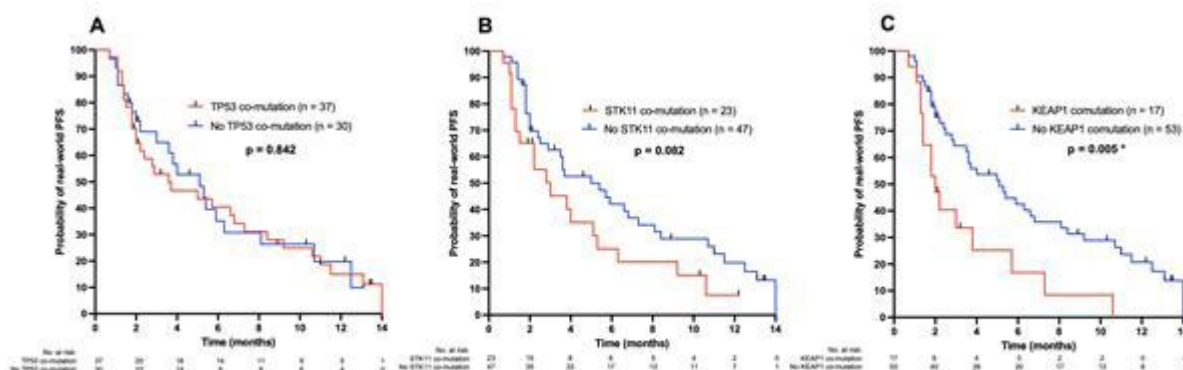


Figure 1: Influence of concurrent TP53, STK11, and KEAP1 mutations on real-world PFS (rwPFS) to sotorasib.

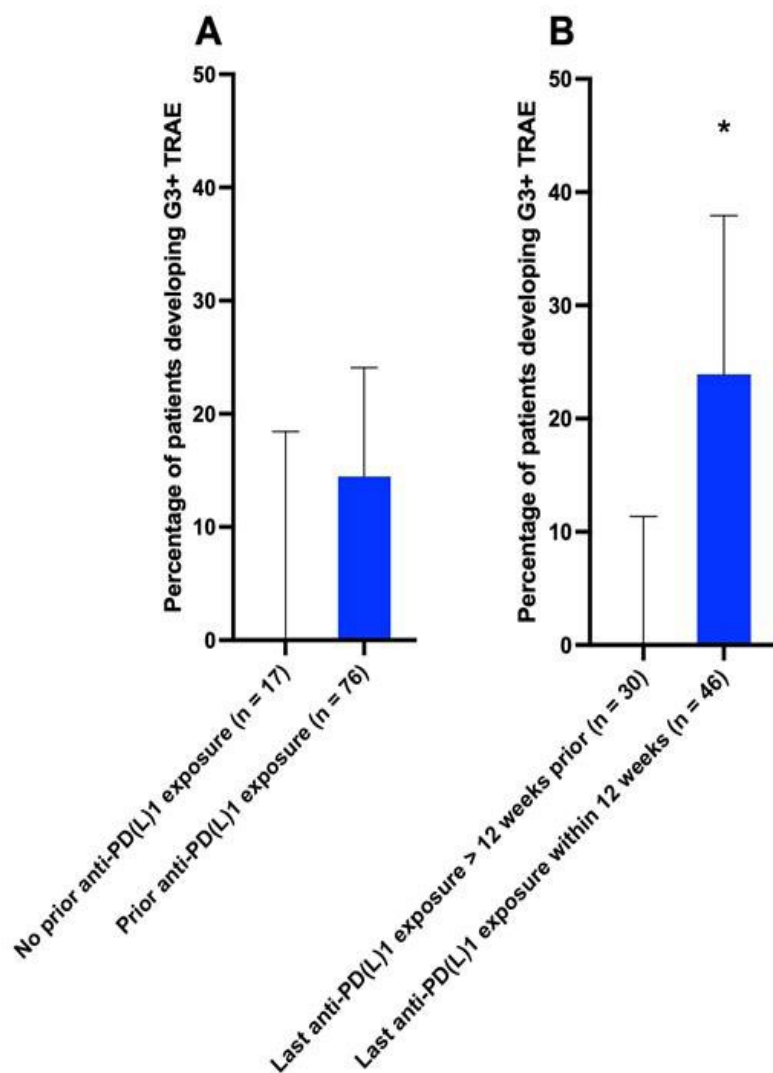


Figure 2: Influence of prior anti-PD(L)1 therapy exposure on incidence of severe sotorasib-related adverse events.

P18: Phase II Trial of Regorafenib and Oral Methotrexate in Previously Treated Advanced KRAS Mutant Non-Small Cell Lung Cancer

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BACKGROUND

Among patients with advanced KRAS mutant NSCLC, there are no approved options for targeted treatment beyond the subtype specific KRAS G12C inhibitors. Using computational modeling, we identified the multi-kinase inhibitor regorafenib and the anti-metabolite methotrexate as a potential therapeutic option in KRAS mutant NSCLC via synergistic inhibition of multiple targets. This study evaluated the efficacy and safety of the combination.

METHODS

A phase II study of regorafenib and oral methotrexate was conducted in patients with metastatic or recurrent KRAS mutant NSCLC who received at least one prior line of systemic therapy. Regorafenib was administered at 80-120 mg daily. Methotrexate was administered twice weekly and dose escalated from 10, 15, to 20 mg during the first cycle if tolerated. Both agents were administered concurrently during weeks 1-3 out of each 4-week cycle. The primary endpoint was progression-free survival (PFS). The study is registered with ClinicalTrials.gov, NCT03520842.

RESULTS

In total, 18 patients with KRAS mutant NSCLC were enrolled. Mean age was 68.9 (SD ± 7.7) years, 12 were female and 6 male, 14 were former and 4 never smoking, and ECOG performance status was 0 in 2 and 1 in 16 patients. KRAS mutation subtypes included G12C (n=6), G12D (n=6), and various other subtypes (n=6; G12V, G12R, G12S, A146V, Q61L). Five patients received regorafenib at a 120 mg starting dose with four discontinuing due to toxicity; after a protocol amendment, 13 patients were treated at an 80 mg starting dose, with 8 dose-escalating to 120 mg after cycle 1. Median PFS was 3.7 months (95% CI 1.9-not reached [NR]) and median overall survival was 10.4 months (95% CI 5.2-NR). Overall, 3 partial responses were observed (2 with KRAS G12D, 1 with KRAS G12R); the objective response rate was 16.7% (95% CI 4.0-41.4). At 8 weeks, the disease control rate was 66.7% (95% CI 41.0-86.7). The most common treatment-emergent grade 3 adverse events were dyspnea (n=3) and hypophosphatemia (n=3). Grade 4 lipase increase occurred in 1 patient, and a treatment-unrelated grade 5 aspiration in 1 patient.

CONCLUSION

Combination treatment of regorafenib and oral methotrexate in patients with KRAS mutant NSCLC was limited due to toxicity. In addition, the study did not meet its primary endpoint. Analysis of circulating tumor DNA (ctDNA) dynamics during study treatment is ongoing.

Table 1. Characteristics of NSCLC with IDH1 or IDH2 Mutations

Features	IDH1 mt Non-Sq (n=136)	IDH1 wt Non-Sq (n=21549)	IDH2 mt Non-Sq (n=24)	IDH2 wt Non-Sq (n=21547)	IDH1 mt Sq (n=9)	IDH1 wt Sq (n=6119)	IDH2 mt Sq (n=2)	IDH2 wt Sq (n=6124)
Smokers ¹	100% (42/42) ¹	90.1% (6235/6921) ¹	100% (9/9) ¹	90.1% (6240/6929) ¹	100% (3/3) ¹	97.30% (2163/2224) ¹	NA ¹	97.26% (2171/2232) ¹
Male	47.8%	46.5%	58.3%	46.6%	66.7%	61.5%	50%	61.4%
PD-L1 ≥1%	85.4%	54.7%	68.2%	54.6%	88.9%	59.7%	0%	59.7%
EGFR mt	5.18%	14.90%	4.167%	14.98%	0%	1.21%	0%	1.22%
KRAS mt	68.15%	33.94%	41.67%	34.03%	0%	3.85%	0%	3.88%
BRAF mt	10.37%	4.95%	12.5%	4.98%	0%	0.92%	0%	0.92%
TP53 mt	56.72%	60.12%	54.17%	60.15%	100%	88.68%	50%	88.85%
ARID1A mt	6.25%	5.05%	26.67%	5.07%	33.33%	6.16%	0%	5.95%

ARID1A (AT-rich interaction domain 1A); BRAF (v-rat murine sarcoma viral oncogene homolog B1); IDH1/2 (isocitrate dehydrogenase enzymes 1 & 2); KRAS (Kirsten rat sarcoma viral oncogene homolog); mt (mutant); Non-Sq (non-squamous histology); PD-L1 (Programmed death-ligand1); Sq (squamous histology); TP53 (tumor protein p53); wt (wild type)

¹Smoking history not available for all patients

P19: IDH1 and IDH2 Mutations in Non-Small Cell Lung Cancer (NSCLC)

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BACKGROUND

Mutations in IDH1 and IDH2 can promote epigenetic dysregulation, leading to oncogenesis via generation of 2-hydroxyglutarate oncometabolites. These mutations represent contexts of vulnerability with the development of novel targeted agents. Ivosidenib is an IDH1 inhibitor approved for IDH1 mutant (mt) leukemia and cholangiocarcinoma and enasidenib is approved for IDH2mt leukemia. IDH1/2mt have been rarely described in NSCLC and represent a potential therapeutic target. Here, we report the incidence and mutational landscape of IDH1/2mt in a large cohort of NSCLC samples.

METHODS

NSCLC samples were analyzed using DNA-based next-generation sequencing (592 genes, NextSeq) or whole-exome sequencing (NovaSeq) and RNA-based whole transcriptome sequencing (NovaSeq). PD-L1 expression was determined using the Dako 22C3 PD-L1 clone with a $\geq 1\%$ threshold for positivity. Immune cell infiltrates were calculated by Microenvironment Cell Populations(MCP)-counter. Significance was determined using chi-square, Fisher's exact and Mann-Whitney U, adjusted for multiple comparisons. Changes were considered statistically significant when both $p < 0.05$ and $q < 0.05$, while $p < 0.05$ but $q > 0.05$ were considered a trend.

RESULTS

Out of 29,177 NSCLC specimens analyzed, IDH1mt were present in 145 tumors (136 nonsquamous, 9 squamous) for an incidence of 0.5%. IDH2mt were less common, identified in 27 tumors (24 nonsquamous, 2 squamous, 1 unclear) for an incidence of 0.1% (Table 1). In IDH1mt NSCLC, co-mutations were common and included KRAS (64%, $q < 0.05$) and BRAF (10%, $p < 0.05$). Among the IDH1mt tumors, co-mutations in TP53 were present in 100% of squamous tumors and 57% of nonsquamous tumors ($p < 0.05$). Similarly, in IDH2mt NSCLC, co-mutations included KRAS (37%, $p > 0.05$), NTRK3 fusions (20%, $p < 0.05$), METmt (11%, $p > 0.05$) and ARID1A (24%, $p < 0.05$). IDH1mt NSCLC tumors had decreased infiltration of B-cells and increased infiltration of myeloid dendritic cells as well as increased expression of CD80, CD274, and HAVCR2, compared to IDH1wt tumors (all $q < 0.05$). IDH2mt NSCLC tumors had increased infiltration of myeloid dendritic cells and macrophages and increased expression of CD80, CD86, and HAVCR2 (all $p < 0.05$). PD-L1 expression was noted in 86% ($q < 0.05$) of IDH1mt NSCLC and 64% ($p > 0.05$) of IDH2mt NSCLC.

CONCLUSION

IDH1 and IDH2 mutations are present at low frequency in NSCLC but frequently occur in the presence of other potential driver alterations including KRAS, NTRK3 fusions, and BRAF. IDH1/2 mutations are also associated with a distinct tumor immune microenvironment. This suggests IDH1/2 mutations are less likely to be primary drivers, but may mediate acquired or intrinsic resistance and combination strategies warrant further investigation.

P20: Prognostic and Predictive Relevance of 3q Amplification in Squamous Cell Carcinoma of the Lung

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BACKGROUND

Amplification (AMP) of 3q is the most common genetic alteration identified in squamous cell carcinoma of the lung (LUSC), it has been described in preinvasive and invasive LUSC and represents one of the most striking molecular differences between LUSC and adenocarcinoma. AMP of 3q is prevalent and carries a prognostic relevance in other squamous cell carcinomas such as head and neck, cervical and esophageal cancers. Many studies evaluated the prognostic value of 3q AMP in LUSC; however, the results are contradicting as they either examined the whole 3q region or 1-2 genes within 3q. We have identified a minimal common region (MCR) of AMP within 3q consisting of 25 genes. In this analysis, we aim to describe the prognostic and predictive relevance of MCR AMP.

METHODS

We conducted an analysis of 476 patients with early-stage (I-III) LUSC from The Cancer Genome Atlas (TCGA) database and extracted molecular and clinical data from cBioPortal and Clinical Data Resources. We analyzed the correlation of MCR AMP with levels of tumor-infiltrating cells and immune checkpoints (ICPs) in The Cancer Immunome Atlas using multiple RNA-based algorithmic scores. We also analyzed the association of MCR status with other common alterations in LUSC such as CDKN2A homozygous deletion, TP53 alteration and PIK3CA amplification.

RESULTS

We identified a MCR consisting of 25 genes within a large amplicon on chromosome 3q, these genes were frequently amplified and several of them signal through PI3K pathway. MCR AMP was detected in 46.4% of the cases and was associated with better disease-specific survival (DSS) (NR vs 9.25 years, 95% CI [5.24-NR]; p=0.011), and progression-free interval (PFI) (8 vs 4.9 years, 95% [3.5-NR]; p=0.020). In multivariable analysis, MCR AMP was associated with significantly improved PFI (HR 0.67, CI 0.47-0.95, p=0.024) and DSS (HR 0.59, CI 0.38-0.94, p=0.025). We analyzed the correlation of MCR AMP with levels of tumor-infiltrating cells and ICPs. PD-L1 expression was higher in MCR-amplified cases, whereas there was a trend toward a higher prevalence of immune-inhibitory cells (such as Regulatory T-cells, cancer-associated fibroblasts, Macrophage M2) in MCR non-amplified cases. MCR AMP was strongly associated with PIK3CA AMP which was detected in 215 (97.3%) of MCR-amplified cases (OR: 4469, p<0.001). CDKN2A homozygous deletion was detected in 70 (31.7%) MCR-amplified cases and 56 (22%) without AMP (OR: 1.64, p=0.021). TP53 alteration was detected in 75 (29.4%) MCR-amplified cases and 82 (37.1%) without AMP (OR: 0.707, p=0.079).

CONCLUSION

MCR AMP within 3q carries a prognostic value and was associated with better PFI and DSS in TCGA LUSC cohort. MCR-amplified cases had higher expression of PD-L1, whereas non-amplified cases had higher prevalence of immune-inhibitory cells. These findings raise the possibility that MCR AMP carries a predictive value as higher PD-L1 expression can predict for a better response to PD-1 pathway inhibitors. These results were obtained from a TCGA cohort mainly composed of Caucasians (69.7%) and patients with early-stage LUSC (98.7%). We are evaluating the prognostic and predictive value of MCR AMP in a diverse patient population of advanced LUSC patients.

P21: HER2/ERBB2 Mutations in Metastatic Non-Small Cell Lung Cancer – Prevalence, Real-World Treatment Patterns and Outcomes from a Clinico-Genomic Database

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BACKGROUND

Human epidermal growth factor 2 (HER2/ERBB2) gene mutations are actionable oncogenic alterations in metastatic non-small cell lung cancer (mNSCLC) following the August 2022 approval of trastuzumab deruxtecan in the US. Given the availability of this novel treatment, we aimed to describe prevalence of HER2 tumor mutations, treatment patterns and outcomes in patients with HER2-mutant mNSCLC in the real-world setting.

METHODS

This retrospective cohort study used Flatiron Health data linked with the Foundation Medicine Clinico-Genomic Database. The study included US adults (age ≥ 18 years) diagnosed with mNSCLC from January 2014 to July 2021 with known DNA next-generation sequencing results including HER2 and excluded those with small cell histology, concurrent malignancy, or absence of clinical data within 180 days of mNSCLC diagnosis. Prevalence, baseline characteristics and treatment patterns were summarized descriptively. Kaplan-Meier analysis was used to assess progression-free survival (PFS) and overall survival (OS).

RESULTS

Of 9206 patients with mNSCLC who had known HER2 testing results, 164 (1.78%) had HER2 tumor mutations without concurrent EGFR mutations. Among these patients with HER2-mutant mNSCLC, mean age was 67 years, 63% were white (6% Asian), 57% were female, and 53% had a history of smoking. Treatment patterns and outcomes by line of therapy are summarized in Table 1. Of 164 patients, 132 (80%) received systemic therapy. The most common first-line regimens were platinum-based chemotherapy (45%) and immunotherapy (IO) in combination with chemotherapy (28%). From first-line therapy initiation, the median (95% confidence interval [CI]) PFS and OS were 5.5 (4.8-6.2) and 13.2 (10.6-18.4) months, respectively. From second-line therapy initiation, the median (95% CI) PFS and OS were 3.0 (2.3-4.2) and 8.2 (6.6-13.2) month, respectively. Across all lines of therapy, HER2 targeted therapy included afatinib monotherapy (n=17), trastuzumab emtansine monotherapy (n=11), trastuzumab with chemotherapy (n=7), trastuzumab emtansine with afatinib (n=1), and trastuzumab deruxtecan (n=1). The use of HER2-targeted treatments increased from less than 16% in first or second lines to 30% in third line.

CONCLUSION

The prevalence of HER2 mutations in mNSCLC in this cohort was consistent with that previously reported at about 2%. Most patients with HER2-mutant mNSCLC received platinum chemotherapy or chemotherapy + IO regimens in the first-line setting. HER2-targeted treatments were mostly used in later lines of treatments. Over half the patients progressed within 6 months after initiating first-line treatments suggesting the need for more effective therapies for patients with this oncogenic driver.

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Dr. Sarah Waliany and Dr. Misako Nagasaka are co-first authors, with Dr. Waliany being the presenting author.

Table 1 Treatment Patterns and Clinical Outcomes in *HER2*-mutant mNSCLC

	LOT1 N=132	LOT2 N=84	LOT3 N=43
Time from initiation of LOT to end of follow-up (months): median (interquartile range)	9 (5,18)	7 (3,13)	8(3, 13)
Treatment groups, N (%)			
Platinum-based chemotherapy (\pm VEGFi or TKI)	60 (45.0)	11 (13.0)	7 (16.0)
Immunotherapy + chemotherapy	37 (28.0)	14 (16.6)	-
Immunotherapy-based therapy*	15 (11.4)	32 (38.0)	8 (18.6)
Non-platinum-based chemotherapy (\pm VEGFi)	9 (6.8)	14 (17.0)	14 (33.0)
HER2-targeted therapy†	11 (8.3)	13 (15.4)	13 (30.3)
VEGF inhibitors	-	-	1 (2.3)
PFS (months): median (95% CI)	5.5 (4.8, 6.2)	3.0 (2.3, 4.2)	4.1 (2.0, 7.2)
OS (months): median (95% CI)	13.2 (10.6, 18.4)	8.2 (6.6, 13.2)	9.7 (6.2, 22.2)

*alone or combination with VEGF inhibitors/another IO

†HER2-targeted therapy included trastuzumab, trastuzumab emtansine, and trastuzumab deruxtecan, and afatanib as monotherapy or combination with other therapy

LOT = line of therapy; VEGF = vascular endothelial growth factor; TKI = tyrosine kinase inhibitors; PFS = progression-free survival; OS = overall survival; CI = confidence interval

P22: Mutations in Spliceosome Genes, SRSF2 and FUBP1, in NSCLC are Associated with Multiple Actionable Driver Mutations, Notably KRAS G12C/V and EGFR L858R as well as STK11/KEAP1 Mutations Without Actionable Driver Mutations

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TITLE

Mutations in spliceosome genes, SRSF2 and FUBP1, in NSCLC are associated with multiple actionable driver mutations, notably KRAS G12C/V and EGFR L858R as well as STK11/KEAP1 mutations without actionable driver mutations. Result's collected from a survey of the cBioPortal GENIE database.

BACKGROUND

Aberrant slicing mechanisms have been identified in a variety of cancers and provide a rich potential field for the development of new cancer therapies. Mutations in five frequently-mutated RNA splicing genes in solid tumors (RBM10, U2AF1, SF3B1, SRSF2 and FUBP1) are also among the most-commonly mutated RNA splicing pathway genes in non-small cell lung cancer (NSCLC). SRSF2 is an auxiliary splicing factor shown to bind exonic pre-mRNA at specific motifs, where it acts as a splicing enhancer. FUBP1 binds to AT-rich exons and mediates exon skipping. FUBP1 mutations are associated with the down-regulation of alternative splicing and MYC-target genes.

METHODS

We surveyed the presence of mutations among 358 genes involved in RNA splicing pathways in NSCLC using the AACR cBioPortal GENIE cohort version 12.0-public version. All unique cases with SRSF2 and FUBP1 mutations were identified and individually analyzed to abstract co-occurring genomic alterations.

RESULTS

A total of 105 unique cases with SRSF2 mutations and 87 with FUBP1 mutations were identified amongst 19,046 cases of NSCLC. Amongst these, 53% were female and 47% were male. Racial composition included 74% White, 8% Asian, 4% Black, <1% Pacific Islander, 6% Other and 8% Unknown individuals. Histology of the NSCLC samples were 74% adenocarcinoma, 5% NSCLC, 16% squamous cell carcinoma, 2% large cell neuroendocrine tumors, and 3% poorlydifferentiated non-small cell carcinoma. Mutations were 74% missense, 11% deletion, 3% insertion, 5% splice-site, 1% fusion, 6% nonsense, and <1% nonstart. Amongst the FUBP1 mutations, 46% co-occurred with established actionable driver mutations, most commonly KRAS G12C (33%) and EGFR L858R (20%). Additionally, amongst the FUBP1 mutations without cooccurring actionable driver mutations, 42% harbored KEAP1 (23%), STK11 (17%), or NFE2L2 (2%) mutations. Amongst the SRSF2 mutations, 35% co-occurred with established actionable driver mutations, most commonly EGFR E746 (14%), KRAS G12C (26%), and KRAS G12V (14%).

Additionally, amongst the SRSF2 mutations without co-occurring actionable driver mutations, 31% harbored KEAP1 (12%), STK11 (3%), or NFE2L2 (10%) mutations. In cases of adenocarcinoma with FUBP1 mutations, 53% co-occurred with actionable driver mutations, the most common of which were EGFR L858R (19%) and KRAS G12C (33%). In cases of adenocarcinoma with SRSF2 mutations, 41% co-occurred with actionable driver mutations, the most common of which were EGFR L746 (19%), KRAS G12C (26%), and KRAS G12V (19%).

CONCLUSION

SRSF2 and FUBP1 mutations in NSCLC are highly-associated with actionable driver mutations, especially KRAS G12C. Additionally 31% had STK11, KEAP1, or NFE2L2 mutations without actionable driver mutations. SRSF2 and FUBP1 mutations in NSCLC potentially serve as a target for RNA splicing inhibition in conjunction with targeted therapies or immunotherapy to enhance treatment outcomes and/or overcome resistance mechanisms.

P23: Mutations in the RNA Binding Motif Protein 10 (RBM10) in NSCLC are Highly Associated with Multiple Actionable Driver Mutations in Particular EGFR L858R or KRAS G12C

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BACKGROUND

RNA splicing defects are emerging molecular hallmarks of cancer. Several of the genes encoding the RNA splicing factors (RBM10, U2AF1, SF3B1) are frequently mutated in NSCLC and may modulate response to EGFR TKIs. RNA binding motif protein 10 (RBM10) is normally associated with splicing repression and can suppress NSCLC progression. RBM10 mutations in NSCLC are associated exon inclusions in NSCLC. Strategies that target RNA splicing can be an adjunct to current NSCLC therapy.

METHODS

RBM10 mutations cases were identified and individually analyzed to abstract co-occurring genomic alterations from approximately 16,913 unique NSCLC cases from the AACR cbiportal GENIE cohort version 12.0-public.

RESULTS

Taken from a survey of the cbiportal GENIE database.

A total of 1182 unique RBM10 cases with mutations were identified accounting for 7.0% of NSCLC. Histologies among the RBM10 mutations were 87.4% adenocarcinoma, 7.7% NSCLC NOS, 4.1% squamous cell carcinoma, 0.7% adenosquamous. Patients were 61.8% female and 37.6% male. The racial composition was: White (79.4%), Asian (7.5%), African American

(2.5%), Native American (0.25%), Others (4.82%), and Unknown (5.58%). Twenty-nine (2.5%) identify as Hispanic. The median number of mutations is 1 (range 0-4). The type of RBM10 mutations were nonsense (35.7%), missense (23.0%), frameshift deletion (18.6%), splice site mutations (16.6%), fusion/rearrangement (0.93%), and frameshift insertion/deletion (0.17%). A total of 882/1204 (73.3%) of RBM10 mutations co-occurred with established actionable oncogenic driver mutations (EGFR del19, L858R, uncommon mutations, exon20ins, KRAS G12X, KRAS G13X, METex14 splicing, BRAFV600E, ALK fusions, ROS1 fusions, RET fusions, NTRK fusions, HER2 amplification and HER2 exon20ins) oncogenic mutations were identified. The three most common actionable driver mutations were: KRAS G12C, EGFR L858R, EGFR other uncommon mutations. Within the larger cbiportal database there were 2196 KRAS G12C mutations and 1191 EGFR L858R mutations, 9.6% and 14.9% of which represent our lung cancer cohort respectively.

Additionally, 33.2% of RBM10 mutations harbored either STK11 (n=73), KEAP1 (n=51), and NFE2L2 (n=7) mutations without co-occurring actionable driver mutations.

CONCLUSION

RBM10 mutations in NSCLC are strongly associated with actionable driver mutations. Targeting RNA splicing alone or in combination with specific on-target inhibition may improve therapeutic efficacy of current targeted and immunotherapy therapy of NSCLC.

P24: Plasma PCSK9 Levels in Patients Receiving Neoadjuvant Pembrolizumab in Resectable Non-Small Cell Lung Cancer (NSCLC)

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BACKGROUND

Neoadjuvant immune checkpoint inhibitor (ICI) therapy prior to surgery in NSCLC has now been reported showing feasibility, safety, and initial anti-tumor activity. However, a substantial number of these patients experienced cancer recurrence indicating potential resistance to immunotherapy which highlights the need for further understanding of resistance mechanisms and predictive biomarkers¹⁻⁵. PCSK9 is a secreted protein that plays a role in regulating plasma cholesterol (LDL) levels. Recently, PCSK9 was shown to play a crucial role in restraining antitumor immunity by limiting T cell accumulation in tumors in part by down-regulating MHC class I on the surface of tumor cells⁶. Plasma PCSK9 levels in the neoadjuvant immunotherapy treatment setting for NSCLC have yet to be investigated.

METHODS

We conducted a single arm, phase II study of neoadjuvant single agent pembrolizumab in patients with clinical stage IB, II, or IIIA NSCLC (TOP1501; NCT02818920) with prior surgical safety/feasibility data reported⁴. Blood specimens were collected from each patient prior to beginning treatment (time 1), prior to surgery after neoadjuvant treatment (time 2), following surgery (time 3), and after completion of adjuvant pembrolizumab (time 4). Following surgical resection, excess tumor underwent disaggregation, viable cryopreservation, and immune profiling. FFPE from resected tumor was sent for genomic analysis. PCSK9 level in plasma samples was measured by colorimetric ELISA according to the manufacturer's instructions (R&D Systems, Minneapolis, MN).

RESULTS

A total of 35 patients were enrolled in the study. 30 patients received neoadjuvant pembrolizumab and 25 underwent lung resection. Major pathologic response (MPR), defined as less than 10% of viable tissue remaining, was observed in 7 specimens (28%) while 9 specimens demonstrated a pathologic response of <50% (36%) defined as sub optimal responders (SOR). There was not statistically significant difference in plasma PCSK9 levels between the MPR and SOR cohort at times 1, 2 or 4. At time 3, mean plasma PCSK9 was 169 (129-207) ng/mL for MPR vs 201 (188-237) ng/mL for SOR, $t(10)=2.8$, $p=0.0179$. For the entire patient cohort, there was notably a significant increase in mean plasma PCSK9 from time 1 to time 2 (mean difference 27 ng/mL, $p=0.0070$, C.I. [5.7, 48]) and time 2 to time 3 (mean difference 42 ng/mL, $p<0.0001$, C.I. [20, 63]). Immune profiling results and genomic analysis in correlation with clinical outcomes and serum PCSK9 values are pending at the time of abstract submission.

CONCLUSION

Plasma PCSK9 levels were shown to increase throughout the treatment course of patient's receiving neoadjuvant pembrolizumab therapy. Patients found to have suboptimal pathologic response at time of surgery had higher plasma PCSK9 levels following surgery than patients who experienced major pathologic response. Correlation of clinical outcomes and PCSK9 level with genomic analysis and immunoprofiling results are pending at time of abstract submission. Additional clinical trials are underway combining ICI therapy with anti-PCSK9 therapy with correlative studies to validate and extend these findings.

P25: Fibroblast Growth Factor Receptor (FGFR) Aberrations in Metastatic Non-Small Cell Lung Cancer (mNSCLC): An Analysis of Prevalence and a Potential Therapeutic Target for Resistance to Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR TKIs)

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BACKGROUND

Lung cancer is the most common cause of cancer-related death globally. Alterations within FGFR genes in de novo mNSCLC have been described, but the data is still limited. FGFR fusions are thought to be rare, but present as an acquired resistance mechanism for EGFR TKIs. These fusions may be actionable with FGFR inhibitors, which could in turn provide another therapeutic target upon EGFR TKI resistance. However, the overall prevalence and genomic landscape of FGFR alterations in mNSCLC patients—as well as in patients who received EGFR TKI treatment—is largely unknown.

METHODS

We used the Tempus database to retrospectively analyze deidentified records from 6,973 adult patients diagnosed with mNSCLC. Patients who underwent tissue-based next generation sequencing (NGS) via the Tempus xT assay (DNA-seq of 595-648 genes, whole exome capture RNA-seq) within 30 days of diagnosis were assessed for prevalence of EGFR and FGFR1-4 alterations, including: pathogenic/likely pathogenic single nucleotide variants (SNVs), deep copy number losses or amplifications ≥ 8 , and fusions. An additional 413 patients with mNSCLC who underwent Tempus xT sequencing after being treated with an EGFR-directed TKI (afatinib, dacomitinib, erlotinib, gefitinib, or osimertinib) for at least 6 months were also identified and the prevalence of FGFR alterations was similarly assessed. All analyses were performed in R version 4.2.0

RESULTS

Of the 6,973 mNSCLC patients in our cohort, 942 (14%, 95% CI 13-14%) were found to have an FGFR alteration: 380 (5.4%) had an alteration in FGFR2 only, 270 (3.9%) in FGFR3 only, 178 (2.6%) in FGFR1 only and 17 (0.2%) in FGFR4 only. A further 97 (1.4%) patients had alterations in multiple FGFR genes. Of 413 mNSCLC patients who underwent sequencing after being treated with an EGFR-directed TKI for at least 6 months, 55 (13%, 95% CI 10-17%) were found to have an FGFR alteration. Of these, 23 (5.6%) had an alteration in FGFR2, 15 (3.6%) in FGFR3, 10 (2.4%) in FGFR1, and 1 (0.2%) in FGFR4. Alterations in multiple FGFR genes were observed for 6 (1.5%) patients. Of the 55 patients in the FGFR-altered population, 33 (60%) were treated with osimertinib, 6 (11%) with erlotinib, 2 (3.6%) with afatinib, 1 (1.8%) with gefitinib, and 13 (24%) were treated with more than one of these TKIs.

CONCLUSION

To our knowledge, this is the first detailed descriptive analysis using real world evidence to provide insight into the prevalence of FGFR alterations in mNSCLC as well as the prevalence of FGFR alterations within a population treated with prior EGFR TKIs. In both cohorts, we observed substantial prevalence of FGFR alterations (13-14%) suggesting that this FGFR altered population merits further inquiry, particularly to understand whether targeting FGFR alterations in both scenarios can provide therapeutic benefit.

P26: Out of Pocket Costs and Receipt of Financial Assistance for Patients with Lung Cancer Prescribed an Oral Targeted Therapy at an Academic Medical Center

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BACKGROUND

With increasing development and approvals of targeted agents for non-small cell lung cancer (NSCLC), a rising proportion of patients with NSCLC are prescribed oral anti-cancer medications (OAMS). Although these therapies have transformed outcomes for patients with NSCLC with oncogenic driver mutations, they are high priced, often with significant cost sharing to the patient compared to intravenous therapies. High out of pocket costs have been associated with lower adherence, more frequent treatment interruptions, and higher treatment abandonment rates, in addition to catastrophic financial repercussions such as depletion of savings and higher rates of bankruptcy. Out-of-pocket costs and payment responsibilities for these medications have historically been opaque to patients and providers alike, with a wide and varying range in cost sharing dependent on specific insurance plans, pharmacy benefits, and access to financial assistance programs. Our study utilized a novel pharmacy database to describe within-drug and between-drug variation in patient monthly copayments and receipt of financial assistance for lung cancer directed OAMS.

METHODS

We conducted a retrospective cohort study including all patients with NSCLC prescribed an OAM through the University of California, San Francisco (UCSF) Specialty Pharmacy between January 1, 2021 and December 31, 2021. The unit of analysis was defined as a patient-drug combination. Copayments were standardized as 30-day costs. Data were extracted through our institution's specialty pharmacy prescribing database and linked to demographic data through the institutional electronic medical record system. Between drug variation in copayments was analyzed using Pearson's chi square tests. A high out of pocket cost was defined as a mean monthly copay of \$150 or more, which is our institution's copay threshold above which pharmacy technicians will screen patients for affordability concerns and connect them to financial assistance programs if they are eligible.

RESULTS

There were 66 total patient-drug combinations over the study period. Mean age of patients was 72 (SD 15), 65% were female, and predominantly White (47%) or Asian (45%) race. Medicare Part D was the primary payor (63%) followed by commercial insurance (23%). The medications prescribed over the study period with a minimum of 5 patients are listed in Table 1. Minimum 30-day copayment for all medications was \$5 or less and maximum copayment was \$3,148. Lorlatinib had the highest percentage of patients who had an average copayment of more than \$150/month. There were no significant differences across medication type in the percentage of patients paying above \$150 per month ($\chi^2=8.98$, $p=0.6$) or the percentage of patients receiving financial assistance ($\chi^2=8.29$, $p=0.69$).

CONCLUSION

There was a high amount of within-drug variation in copayments for lung cancer OAMS within a single integrated specialty pharmacy program. Access to financial assistance programs may help mitigate the repercussions of rising cost of oral TKIs for patients with lung cancer. Institutions should ensure patients with lung cancer who have concerns about affording their medications are connected to these assistance programs in a timely and equitable manner.

Table 1: Oral anti-cancer medications for lung cancer at the UCSF Specialty Pharmacy from 1/1/2021-12/31/2021*

Medication name	Number (% of total) of patients	Maximum 30-day copayment	Percentage of patients with mean 30-day copay above \$150	Percentage of patients who received financial assistance
Osimertinib	32 (49%)	\$3,050	16%	22%
Afatinib	6 (9%)	\$2,572	33%	0%
Alectinib	5 (8%)	\$1,715	20%	40%
Capmatinib	5 (8%)	\$2,454	20%	20%
Erlotinib	5 (8%)	\$5	0%	40%
Lorlatinib	5 (8%)	\$3,148	60%	20%
Total	58 (88%)	\$3, 148	20%	23%

*Minimum copayment was \$5 or less for each medication

P27: Clinicogenomic Characteristics of EGFR-Mutant Non-Small Cell Lung Carcinoma with CNS Metastases

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BACKGROUND

Central nervous system (CNS) metastases in non-small cell lung carcinoma (NSCLC) confer potentially debilitating clinical outcomes and poorer prognosis. Limited data are reported on the genomic landscape of CNS metastases. We assessed the clinicogenomic characteristics and outcomes of EGFR-mutant (EGFRm) patients (pts) with CNS metastases.

METHODS

We performed an institutional retrospective analysis of EGFRm NSCLC pts with available CNS tumor samples that underwent next-generation sequencing using MSK-IMPACT. Clinical characteristics and outcome data were obtained from the hospital's electronic database.

RESULTS

Ninety pts were included, of which 69 (76%) were females, with a median age of 59 years (range: 36-87). Eighty-four patients (93%) have non-squamous histology, 57% (n=51) were never smokers, 56% (61% (n=50) with leptomeningeal carcinomatosis (LM) and 44% (n=40) with brain metastases (BM) only. EGFR driver alterations were n=43 exon 19del, n=27 L858R, n=10 atypical, n=8 exon 20 insertion, and n=2 others. The median survival from the development of BM only and LM was 2.5 years and 1.9 years respectively, p=0.044.

Enrichment in RAC1, MET and CARD11 was seen in the BM only as compared to LM (24% vs 8%, p=0.01, 19% vs 0%, p=0.01 and 24% vs 8%, p=0.02). Forty-one pts with paired systemic and CNS tumor samples were identified. Enrichment of RAC1, CDKN2A, CDKN2B, and NKX3-1 was seen in the CNS tumor samples as compared to systemic tumor samples (0% vs 15%, p=0.028, 17% vs 49%, p=0.009, 17% vs 49%, p=0.009, and 2% vs 22%, p=0.017).

CONCLUSION

To our knowledge, this is the largest study investigating genomic profiling of CNS metastases in EGFRm pts. Pts with LM have significantly shorter median survival after developing CNS metastases highlighting the need for better treatment intervention for these pts.

P28: Inhibition of ATR can Target Osimertinib Resistance in EGFR-Mutated NSCLC

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BACKGROUND

Lung cancers with strong oncogene drivers treated with tyrosine kinase inhibitors (TKIs) inevitably develop therapeutic resistance and clinical progression. As newer such inhibitors have become more potent and selective, mechanisms of resistance have become more obscure, varied, and difficult to target. Osimertinib resistance in EGFR mutant lung cancer is the most classical manifestation of this problem. Multiple strategies to treat or delay resistance – notably adding chemotherapy to osimertinib upfront or based on circulating tumor (ct)DNA – are under clinical investigation. Enhanced DNA damage and deficient DNA repair is selected for by cancer cells to facilitate somatic diversification, which may in turn drive tumor resistance. We hypothesized that these processes lead to osimertinib resistance and would therefore be targetable by newer-generation DNA damage repair (DDR) pathway inhibitors. We therefore investigated the efficacy of drugs targeting the DDR in osimertinib-resistant, EGFR-mutated lung cancer cell lines.

METHODS

We generated osimertinib-resistant cell lines with different baseline EGFR mutations and sequenced them to confirm they harbored no previously observed bypass-tract mutation or known resistance mechanism. We confirmed that osimertinib resistance was stable and not mediated by a reversible drug-tolerant persistent state. We then treated these cell lines with a panel of clinical-grade inhibitors of the DDR, including inhibitors of PARP, ATM, ATR, CHK1, and compared responses with and without osimertinib and to platinum chemotherapy as a control. We also generated siRNA-targeted knock-down of mediators of tumor evolution such as APOBEC and measured impacts on DNA repair processes and cell-cycle progression in resistant versus sensitive cells.

RESULTS

We obtained cell lines with osimertinib IC50s ranging from 4x to 1000x parental cells; we also generated long-passaged controls to rule out effects of long-term cell culture. We observed a linear increase in sensitivity to ATR inhibition with increasing resistance to osimertinib. This relationship was not found for platinum chemotherapy or for other DDR inhibitors. We did not observe an abrogation of this effect with APOBECA3A knock-down, suggesting some other sensitizing process is involved. Measures of active DNA repair and cell-cycle control indicated broad differences between osimertinib-resistant and -sensitive cell lines related to DNA repair processes.

CONCLUSION

Osimertinib-resistant cell line models have differential sensitivity to ATR inhibitors, but not to other inhibitors of DNA repair or to platinum chemotherapy. The basis for this specific sensitivity to ATR inhibitors remains under investigation, but may form the basis of new approaches to target TKI-resistant, EGFR-driven lung tumors.

P29: The LAG-3/FGL1 Axis is a Dominant Immune Evasion Pathway in NSCLC Modulated by Hypoxia

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BACKGROUND

LAG-3 is an inhibitory receptor expressed on the surface of activated T-cells and associated with T-cell dysfunction. Engagement of LAG-3 by Fibrinogen-like 1 (FGL1) mediates T-cell suppression and favors tumor immune evasion in experimental models. Monoclonal antibodies targeting LAG-3 are being evaluated as anti-cancer treatment in patients with NSCLC. However, the expression, clinical significance and modulation of LAG-3/FGL1 in human NSCLC remains uncertain.

METHODS

Using Imaging Mass Cytometry (IMC) we simultaneously mapped 37 tumor and immune cell markers to characterize the LAG-3/FGL1 pathway, associated immune contexture and local hypoxia in 119 primary baseline NSCLC samples from two independent cohorts of patients treated with standard chemotherapy (Cohort#1, n=57) or PD-1 axis blockers (Cohort#2, n=62). The markers included were LAG-3, FGL1, DNA1, DNA2, histone H3, cytokeratin, vimentin, PD-L1, PD-L2, VISTA, CD47, 2M, CD56, CD8, CD4, CD25, CD27, CD20, CD68, CD45RO, CD45RA, EOMES, TOX1/2, TCF-7, TIM-3, CD137, PD-1, FOXP3, TBET, GZB, Ki-67, DC-lamp, CD68, CC3 (Cleaved Caspase-3), ARG-1, HIF1 and CAIX (carbonic anhydrase-9). Single-cell analysis from segmented tissue samples was conducted using unsupervised clustering. To assess the role of hypoxia in T-cell dysfunction and FGL1 expression, we exposed cultured PBMCs or A549/H1975 lung tumor cells to 1% O₂ and evaluated T-cell functional profiles after repetitive TCR stimulation by flow cytometry and FGL1 protein levels using immunoblot.

RESULTS

FGL1 protein was expressed in tumor cells from 18.4% of the samples across the cohorts. High FGL1 expression in malignant cells was associated with higher levels of local effector CD8⁺ tumor infiltrating lymphocytes (TILs) with an activated/dysfunctional phenotype characterized by high expression of CD45RO, CD137, PD-1, LAG-3, TIM-3, EOMES and TOX. Elevated FGL1 expression occurred predominantly in CK⁺ tumor cells with high levels of proliferation (Ki-67), apoptosis (CC3) and hypoxia markers (HIF1 and CAIX). Elevated expression of FGL1 in pre-treatment samples was associated with shorter survival after PD-1 axis blockers. In vitro experiments using experimental hypoxia induced prominent changes in the functional profile of CD8⁺ T-cells and upregulated FGL1 protein in lung tumor cell lines.

CONCLUSION

The LAG-3/FGL1 pathway is expressed in ~18% NSCLCs associated with local effector TILs dysfunction, tumor-cell hypoxia and reduced sensitivity to PD-1 axis blockers. Experimental hypoxia is sufficient to alter T-cell function and induce FGL1 expression in tumor cells. Together, our results support the LAG-3/FGL1 axis as a dominant immune evasion pathway in a subset of NSCLCs and modulated by tumor microenvironment hypoxia.

P30: NRG1 Fusions in Non-Small Cell Lung Cancer (NSCLC)

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BACKGROUND

NRG1 fusions are rare but actionable events that occur across tumor types including non-small cell lung cancer (NSCLC). NRG1 has an EGF-like domain that activates ErbB receptors, notably HER3, prompting heterodimerization, usually with HER2, and activation of relevant downstream signaling pathways. Agents targeting the HER2/HER3 pathway have shown early clinical promise in NRG1 fusion-positive cancers: both zenocutuzumab and seribantumab have FDA Fast Track Designation for tumors with NRG1-fusions. Here, we update the incidence and characterization of NRG1-fusion positive NSCLC.

METHODS

Samples submitted for clinical molecular profiling that included RNA-sequencing (Archer Dx or Caris MI transcriptome) were retrospectively analyzed for NRG1 fusion events. All NRG1 fusions with ≥ 3 junction reads were identified for manual review and for characterization of fusion class, intact functional domains, domain prediction, breakpoints, frame retention and co-occurring alterations by next-generation sequencing.

RESULTS

There were 69 unique NRG1 fusion-positive NSCLC samples identified. Patients with NRG1 fusion-positive NSCLC had a median age of 69 years (range 44-85), were more likely to be female (58%), and most cases had adenocarcinoma histology (81.2%). Among the 69 NSCLC tumors, there were 27 unique fusion partners. The most common fusion partners were CD74 (36.7%), SLC3A2 (17.7%), and SDC4 (6.3%). Co-mutations in TP53 were common (51%); other genes often co-mutated included ARID2 (9%), ATM (9%), and GNAS (4%). Only 32.4% of NRG1 fusion-positive NSCLC had PD-L1 $\geq 1\%$ and only 13% had high tumor mutational burden.

CONCLUSION

NRG1 fusions are rare but actionable genomic events in NSCLC but there is striking heterogeneity within this family of alterations. The clinical impact of this heterogeneity on response to targeted agents warrants close attention.

P31: GUK1 is a Novel Metabolic Liability in Oncogene-Driven Lung Cancer

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BACKGROUND

There is a longstanding desire to take therapeutic advantage of dysregulated metabolic states in cancer. While it has been appreciated that lung tumors rewire their cellular metabolic networks to support unrestrained proliferation, metabolic vulnerabilities have largely not been explored in the context of specific onco-genotypes. This represents a major gap in our understanding of how different oncogenic drivers in non-small cell lung cancer (NSCLC) confer reliance on discrete metabolic networks to sustain tumor growth. The goals of this project are (1) to investigate metabolic dependencies in distinct molecular subtypes of lung cancer and (2) to elucidate how metabolic reprogramming drives resistance to targeted therapy.

METHODS

To elucidate metabolic vulnerabilities in oncogene-driven lung cancer, we are using integrative metabolomics approaches in patient-derived cell culture models, orthotopic mouse models, and tumor specimens collected before and after the development of resistance to tyrosine kinase inhibitors (TKIs).

RESULTS

Using patient-derived cell culture models and tumor specimens collected from patients with ALK-positive (ALK+) NSCLC, we identified that lung tumors with ALK rearrangements harbor a unique metabolic signature marked by reliance on anabolic nucleotide pathways. A phosphoproteomic screen in ALK+ patient-derived cells identified a novel metabolic target of ALK signaling, GUK1, the only known enzyme responsible for GDP synthesis. We show that ALK binds to and phosphorylates GUK1 and that ALK-mediated GUK1 phosphorylation augments GDP/GTP nucleotide biosynthesis. Steady-state and tracing metabolomic studies demonstrate that ALK inhibition and GUK1 phosphomutant are epistatic in guanine nucleotide production. Molecular dynamic modeling suggests that phosphorylation of GUK1 alters the dynamics of active site closure to enhance substrate processivity and protects GUK1 from a non-catalytic confirmation. Introduction of phosphomutant GUK1 into ALK+ patient-derived cell lines results in decreased tumor proliferation in vitro and in vivo in xenograft models. Spatially resolved mass spectrometry imaging of tumor specimens from ALK+ patients demonstrates significant enrichment of guanine nucleotides in ALK+ and phospho-GUK1+ tumor cells. We identified that other oncogenic fusion proteins in lung cancer also regulate GUK1 phosphorylation, highlighting the need to further characterize GUK1 as a metabolic liability more broadly in NSCLC. Furthermore, a subset of patient-derived cell lines with resistance to ALK TKIs exhibits increased expression and phosphorylation of GUK1, indicating that regulation of this metabolic enzyme may play a role in mediating acquired resistance.

CONCLUSION

GUK1 is a novel metabolic liability in oncogene-driven lung cancers. We anticipate these studies will pave the way for the development of new therapeutic approaches by exploiting metabolic vulnerabilities in oncogene-driven lung cancers.

P32: Durable Complete Response in Leptomeningeal Disease (LMD) of EGFR Mutated Non-Small Cell Lung Cancer (NSCLC) to Amivantamab, an EGFR-MET Receptor Bispecific Antibody, After Progressing on Osimertinib

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BACKGROUND

Amivantamab is the first monoclonal antibody with bispecific binding to EGF and MET receptors, approved for locally advanced metastatic NSCLC patients harboring EGFR exon 20 insertion after progression on platinum-based chemotherapy. However, its role in patients with CNS involvement which affects one-third of EGFR-mutant NSCLC patients or other EGFR mutation subtypes, is unclear. Here, we present a case of a patient with an atypical EGFR mutation who continues to have a significant response to single-agent amivantamab following progression on osimertinib.

A 67-year-old male presented with recently diagnosed advanced NSCLC. Imaging studies, including a CT body scan and MRI brain, showed a speculated 7.7 cm right upper lung lesion, hilar and subcarinal lymphadenopathies, along with multiple bone metastases without CNS involvement. A biopsy of the primary lung mass confirmed poorly differentiated squamous cell carcinoma with PD-L1 IHC 70%. Tissue next-generation sequencing (NGS) demonstrated EGFR G719A (exon18 substitution) mutation. Osimertinib was started and continued until he was admitted for drug-induced pneumonitis 2 months later when a CT angiogram chest also found new diffuse pericardial thickening and nodularity, suggestive of progressive disease. He received 2 cycles of carboplatin and paclitaxel followed by ipilimumab and nivolumab. Repeat scans in 10 weeks showed progression of disease with new parenchymal disease and LMD. Immunotherapy was discontinued, and the patient was started on amivantamab monotherapy. While on amivantamab 1050mg IV weekly followed by every 2 weeks at week 5, the patient only experienced a mild rash. Otherwise, he tolerated the drug with good performance status. The initial response was shown in a 6-week follow-up scan, with decreased leptomeningeal enhancement and a decrease in the size of parenchymal lung lesions and lymphadenopathies. Repeat circulating tumor DNA NGS also showed a significant reduction of the highest variant allele from 25.6% (EGFR G719A) to non-detectable. 6 months after starting amivantamab, the patient was found to have complete resolution of CNS disease, including LMD. Drastic improvement in his functional status was observed during this period; from wheelchair-bound at the time of progression prior to amivantamab use to him ambulating without assistance and driving independently. He has received amivantamab for more than 14 months, and his scans continue to show durable responses in the primary lung lesion with no evidence of CNS disease.

DISCUSSION

Amivantamab monotherapy was previously suspected to have a limited clinical benefit to CNS metastases due to poor blood-brain barrier penetration of the large-sized antibody. However, our case has shown a durable complete response in CNS disease in a patient with an atypical EGFR mutated NSCLC with LMD that progressed on osimertinib. Further studies are warranted to explore the clinical utility of amivantamab monotherapy in treating patients with CNS metastases or other rare EGFR mutations who progressed on conventional TKIs.

P33: SMARCA4-Deficient Undifferentiated Lung Carcinoma with Additional Microsatellite Instability Mixed Response to Pembrolizumab Followed by Hyperprogression – A Cautionary Tale Highlighting the Pitfalls to Tumor Agnostic Drug Approvals

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BACKGROUND

Pembrolizumab is a PD1 inhibitor and the first drug approved in a tumor agnostic fashion for any tumor type expressing high microsatellite instability (MSI-H). Significant improvements in survival have been seen with first-line pembrolizumab treatment of MSI-H tumors of gastrointestinal origin compared to chemotherapy, but literature is significantly less robust regarding first-line pembrolizumab treatment of MSI-H lung cancers. SMARCA4-deficient undifferentiated tumors (SMARCA4-UT) are rare tumors occurring most commonly in middle aged male smokers that, no matter which organ they are associated with, have poor outcomes and respond poorly to most contemporary treatments. These have only recently begun to be categorized as a histologically distinct entity from non-small cell lung cancer harboring the same mutation. Here we present a case report of a SMARCA4-deficient Undifferentiated Tumor (SMARCA4-UT) lung carcinoma with additional microsatellite instability (MSI-H) treated with first-line pembrolizumab. To our knowledge, this is the first case study to describe the clinical course of an undifferentiated tumor type with coexisting SMARCA4 deficiency and microsatellite instability.

METHODS

A 63-year-old woman's treatment for mediastinal SMARCA4-UT MSI-H, PDL1 low stage IIIC cT3 pN3 was retrospectively followed. Initial MDTB recommendations including definitive chemo-RT with subsequent consolidation durvalumab were not ideal due large primary tumor and low performance status. We discussed her unique tumor molecular profile, harboring a dMMR/MSI-H tumor (with PD-L1 positivity) which portends an inherent sensitivity to immune checkpoint inhibitors, despite paucity of supporting evidence for site-specific lung cancer treatment. She was started on upfront immune checkpoint inhibitor (ICI) therapy with pembrolizumab every 3 weeks.

RESULTS

After 2 cycles the patient noted symptomatic improvement in her breathing and pain. Repeat CT NTAP prior to cycle 5 with an overall mixed response, showing stable disease in the lung. She had cycle 6 of therapy delayed due to 2 episodes of grade 2 immune-medicated hepatitis. She presented prior to late cycle 6 with significantly worsened functional status and hyperprogression apparent on repeat imaging. Following discussion with tumor board and family, the patient decided to transition to hospice care and symptom targeted treatment.

CONCLUSION

Despite MSI-H status and SMARCA4 deficiency, our patient which high tumor burden had a poor response to first line pembrolizumab with mixed response followed by hyperprogression. Overall survival from diagnosis was 7 months, consistent with median survival time of SMARCA4-UT. Given the limited literature on dMMR/MSI-H lung cancer, this case may serve as an anecdotal but cautionary tale highlighting the pitfalls to tumor agnostic drug approvals (such as pembrolizumab for all dMMR/MSI-H cancers). Extrapolating from other tumor types' outcome data may not translate as optimistically to NSCLC. Further review of population-based data on dMMR/MSI-H NSCLC and SMARCA4-UT is warranted to elucidate outcomes of PD-1 inhibitor treatment on these tumor types

P34: BASECAMP-1: Leveraging Human Leukocyte Antigen A (HLA-A) Loss of Heterozygosity (LOH) in Solid Tumors by Next-Generation Sequencing (NGS) to Identify Patients With Relapsed Solid Tumors for Carcinoembryonic Antigen (CEA) and Mesothelin (MSLN) Logic-Gated Tmod™ Chimeric Antigen Receptor (CAR) T-Cell Therapy

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BACKGROUND

Chimeric antigen receptor T-cell therapy has demonstrated clinical efficacy in hematologic cancers (Locke, et al. NEJM 2022). However, translating engineered T-cell therapies to solid malignancies proves challenging due to the lack of tumor-specific targets that can distinguish cancer cells from normal cells. Previously, the use of a CEA T-cell receptors and MSLN CARs both resulted in dose-limiting on-target, off-tumor toxicities (Parkhurst, et al. Mol Ther 2011; Haas, et al. Mol Ther 2019).

Tmod CAR T-cell therapy addresses these challenges by leveraging dual-signaling receptors that target tumor cells, while leaving healthy cells intact (Hamburger, et al. Mol Immunol 2020; DiAndreth, et al. Clin Immunol 2022). The activator receptor recognizes an antigen, such as MSLN or CEA, on the surface of the tumor cells that may also be present on normal cells (Figure 1). Specificity for tumor cells is provided by a blocker that recognizes a second surface antigen lost only in tumor cells (Sandberg, et al. Sci Transl Med 2022; Tokatlian, et al. J Immunother Cancer 2022). LOH is observed at the HLA-A locus in ~23% of non-small cell lung cancer in Tempus and other data sets, and similar frequencies are observed in other solid tumors (Hecht, et al. J Clin Oncol 2022). As such, HLA LOH offers a promising tumor versus normal discriminator target for CAR T-cell therapy.

BASECAMP-1 is a currently enrolling observational study with the following key objectives: 1) to identify patients with somatic HLA-A LOH eligible for Tmod CAR T-cell therapy, and 2) subsequent apheresis and manufacturing feasibility for future EVEREST Tmod CAR T-cell trials.

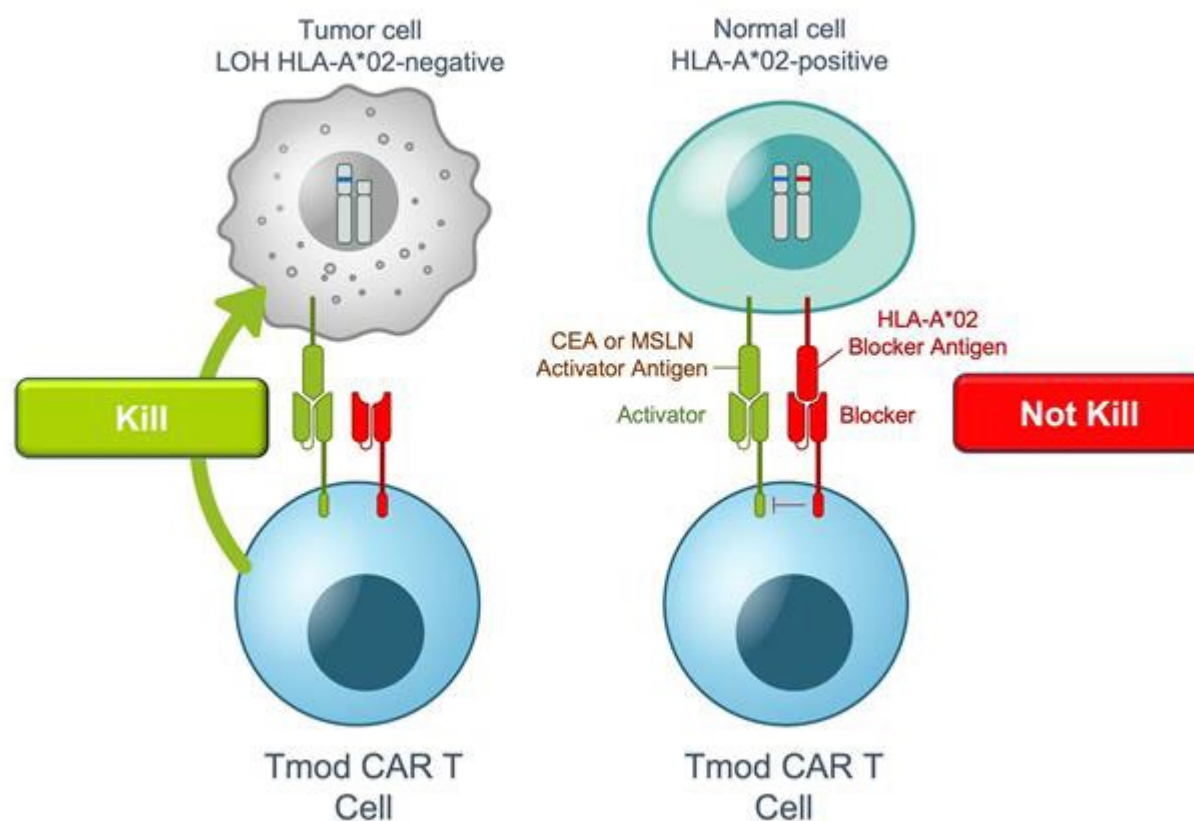
METHODS

BASECAMP-1 (NCT04981119) eligibility has 2 parts. Patients will be initially screened to identify germline HLA-A*02 heterozygosity. Primary archival tumor tissue from the identified patients with germline HLA-A*02 heterozygosity will be analyzed for somatic tumor HLA-A*02 LOH by Tempus xT NGS. If the tumor demonstrates HLA-A*02 LOH and the patient is eligible after screening, the patient will undergo leukapheresis and be followed for relapse. Banked T cells will be available for the autologous EVEREST Tmod CAR T-cell therapy interventional study at the time of relapse.

RESULTS

With a data cutoff date of 11/21/2022, 152 patients have been screened. Fifty-six HLA-A*02 heterozygous patients (42% of resulted subjects) and 5 LOH patients (23% of resulted subjects) have been identified, consistent with predicted population frequencies of A*02 and LOH. LOH patients are being scheduled for apheresis.

Figure 1. Logic-gated CAR T with the goal of reducing toxicity: CEA or MSLN (activators) and HLA-A*02 (blocker)



CAR, chimeric antigen receptor; CEA, carcinoembryonic antigen; HLA, human leukocyte antigen; LOH, loss of heterozygosity; MSLN, mesothelin.

P35: A Case and the Landscape of Coexisting EGFR Mutation in Non-Small Cell Lung Cancer (NSCLC) with Microsatellite Instability (MSI) High and Tumor Mutation Burden (TMB) High Traits

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BACKGROUND

Front-line epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) therapy is the standard of care for lung cancer patients harboring EGFR mutations most commonly exon 19 deletion or L858R mutation. MSI high (MSI-H) and TMB high (TMB-H) are associated with favorable response to immune checkpoint inhibitor therapy. EGFR mutated NSCLCs usually have low TMB and MSI-stable tumors.

METHODS

A 42-year-old former smoker (22.5 pack year) male with no significant past medical history presented to the emergency room with recurrent chest pain and dyspnea on exertion. CT chest showed a spiculated right upper lobe lung nodule measuring 15mm with concern for lymphangitic carcinomatosis in addition to pulmonary embolism. Bronchoscopy-guided fine needle aspiration of 11L lymph node (LN) revealed adenocarcinoma of the lung (TTF-1+, PD-L1 IHC 70% on tumor cells, Sp263 assay). Further imaging studies showed diffuse metastatic disease including brain and lymph nodes. The patient underwent left craniotomy and metastatic brain tumor resection followed by adjuvant gamma knife therapy.

Tissue next-generation sequencing (NGS) of the LN showed EGFR exon 19 deletion [L747_P753delinsS, variant allele frequency (VAF) 15%] and other functional mutations including MLH1 (VAF 21%), TP 53 (VAF 22%), APC (VAF 23%), TSC2 (VAF 15%), INPP4B (VAF 13%), and ERCC5 (VAF 5%). Given that no germline mutations were found, the tumor harbored somatic MLH1 mutation without Lynch syndrome. The tumor had MSI-H and TMB-H, (TMB, 17.7 mut/Mbp) traits. Blood circulating tumor DNA NGS also detected EGFR exon 19 deletion (L747_P753delinsS, VAF 0.6%) as well as MSI-H, and TMB-H (TMB, 16.3 mut/Mbp) traits. Functional mutations detected in blood NGS include MLH1 (VAF 0.5%), TP53 (VAF 0.6%), and PTEN (VAF 0.4%). The patient started osimertinib 80 mg daily. He is tolerating the treatment well with good clinical response. Of note, tissue NGS and RNA sequencing of the metastatic brain lesion showed ERBB2(HER2) copy number gain and transcriptomic overexpression.

Publicly accessible data from cBioportal was utilized to investigate the landscape of EGFR mutation in relation to MSI and TMB status. Among 1,717 samples of EGFR mutated NSCLC, MSI and TMB status were reported for 341 samples. Excluding 16 (5%) MSI indeterminate samples, 325 (95%) had MSI stable (MSS) tumors. For 325 samples with EGFR mutation and MSS, the median TMB was 3.91 (Q1:2.59, Q3:6.05) and 12 (3.6%) samples were TMB-H (>10 mut/Mbp).

Among 5,497 samples of EGFR wildtype NSCLC, MSI and TMB status were reported for 470 samples. Excluding 7 (2%) MSI indeterminate samples, 1 had MSI-H tumor with TMB of 29.4 mut/Mbp and 462 (98%) had MSS tumors. For 462 samples with EGFR wildtype and MSS trait, median TMB was 5.18 (Q1: 2.59, Q3: 8.64) and 99 (21.4%) samples had TMB-H trait (>10 mut/Mbp).

CONCLUSION

In summary, we report, for the first time, a rare case of EGFR-mutated NSCLC with MSI-H and TMB-H traits currently responding well to osimertinib.



ATTENTION PATIENT ADVOCATES: We are recruiting PRAs for STARS 2023!

The **IASLC Supportive Training for Advocates on Research & Science (STARS)** program aims to increase the number of patient research advocates (PRAs) equipped to provide accurate scientific translation in their online or real-life groups for patients with lung cancer and their caregivers, and to provide the patient perspective for lung cancer research and policy.

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April 2, 2023**

The STARS 2023 Program – (all virtual, June – October 2023)

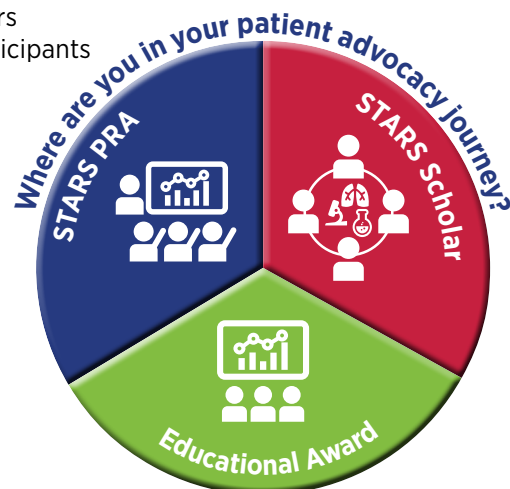
Eligibility:

- ★ Any patient with lung cancer or caregiver interested in research advocacy (including PRAs who participated in one previous STARS program)
- ★ Up to 15 Patient Research Advocates (PRAs) will be selected via competitive application with goal of global representation

Program Elements:

- ★ Interaction with STARS Mentors
- ★ Participate in educational and networking activities June through October
- ★ IASLC Webinar (open to all interested patient advocates) with real-time interpretation in select other languages
 - 2 webinars (open to STARS participants) with Key Opinion Leaders (KOLs) as speakers
 - 3 networking sessions with STARS participants
 - Research Advocate Network online learning modules
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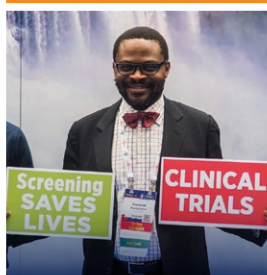
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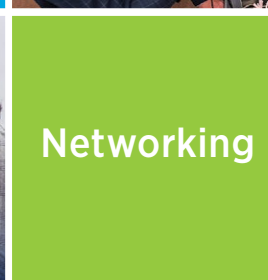
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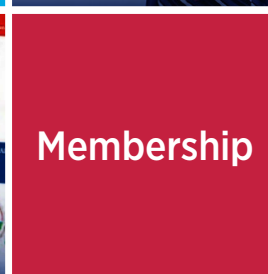
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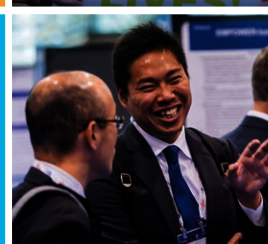


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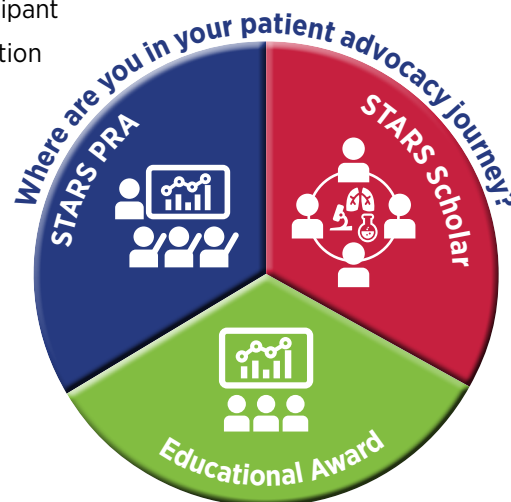
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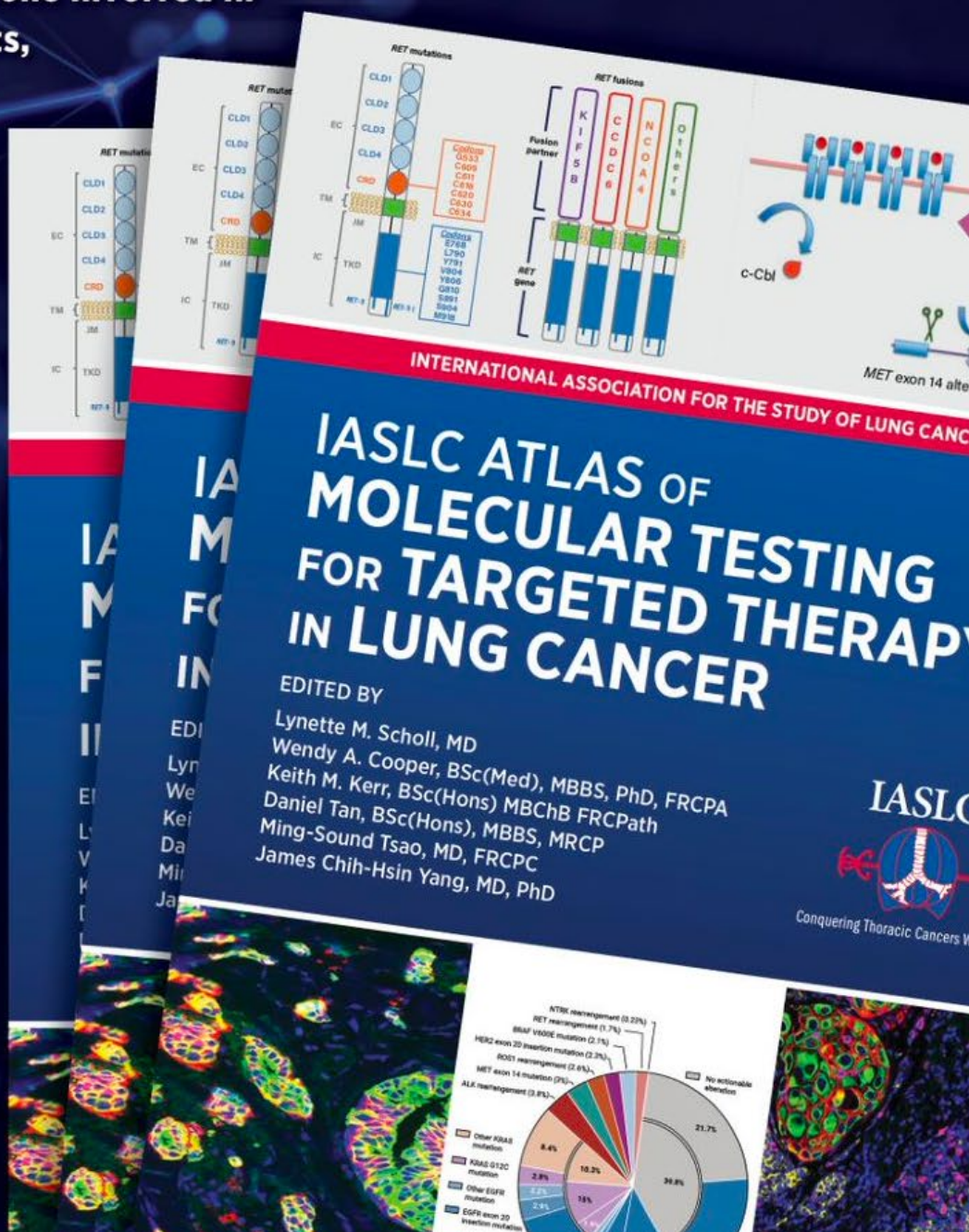
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IASLC 2023

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IASLC 2023 Hot Topic Meeting: Small Cell Lung Cancer

April 5-7, 2023
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