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EPICS

EPICS – Lung Cancer in 2021 and Beyond

December 3–4, 2021

Report Contents

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Meeting Snapshot

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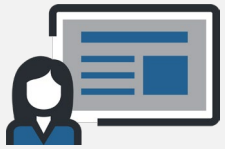
VIRTUAL CLOSED-DOOR ROUNDTABLE

DATE:
December 3–4, 2021



DISEASE STATE AND DATA PRESENTATIONS by key experts

INSIGHT REPORT including postmeeting analyses and actionable recommendations

PANEL: Key experts in lung cancer
- > 8 from US
- > 1 from Canada

LUNG CANCER-SPECIFIC DISCUSSIONS on therapeutic advances and their application in clinical decision-making

Panel Consisting of 8 US and 1 Canadian Lung Cancer Experts

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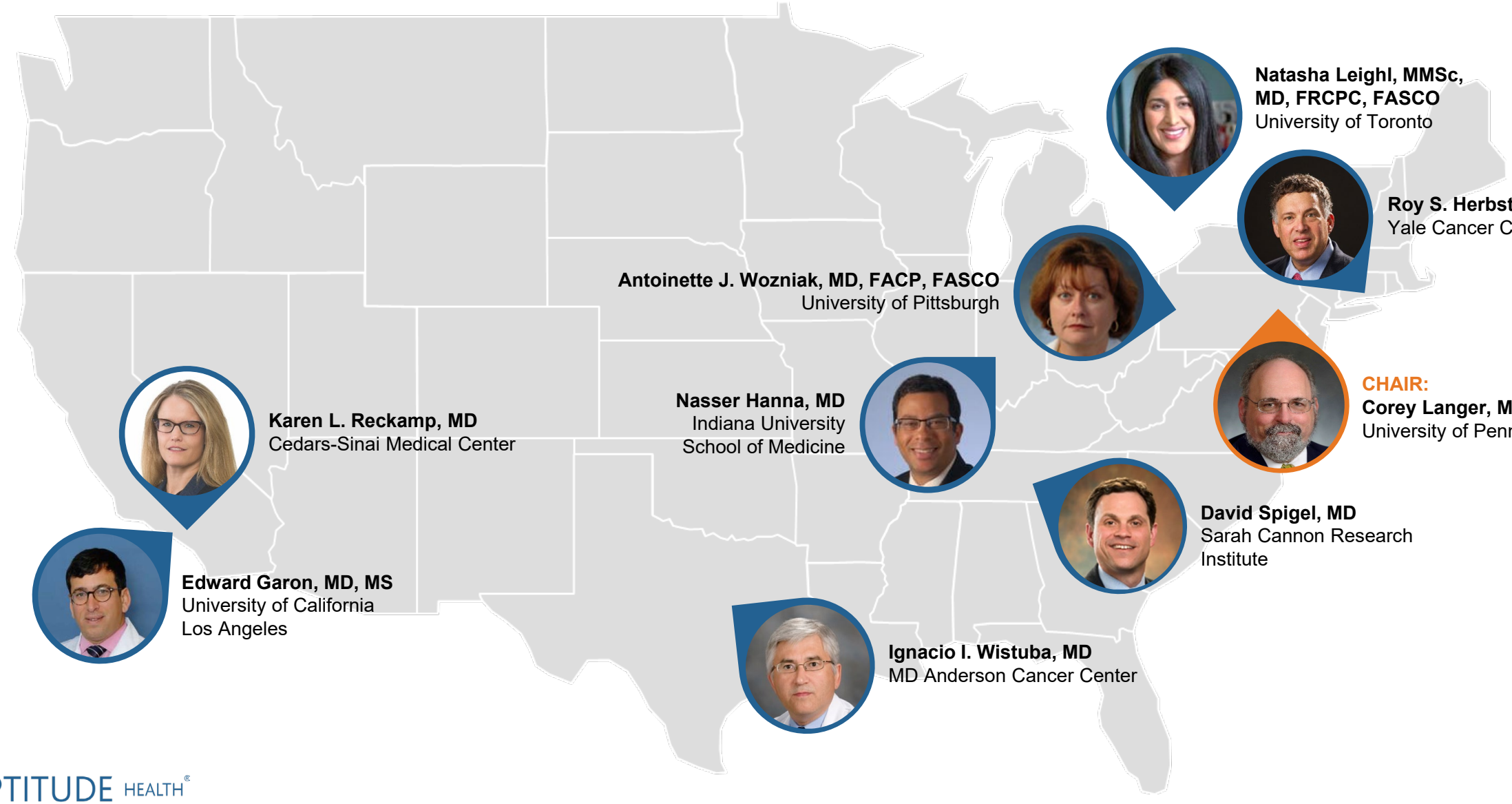

Natasha Leighl, MMSc, MD, FRCPC, FASCO
University of Toronto

Roy S. Herbst, MD, PhD
Yale Cancer Center

Antoinette J. Wozniak, MD, FACP, FASCO
University of Pittsburgh

CHAIR:
Corey Langer, MD, FACP
University of Pennsylvania

Nasser Hanna, MD
Indiana University School of Medicine

Karen L. Reckamp, MD
Cedars-Sinai Medical Center

David Spigel, MD
Sarah Cannon Research Institute

Edward Garon, MD, MS
University of California Los Angeles

Ignacio I. Wistuba, MD
MD Anderson Cancer Center

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Meeting Agenda – Day 1 (1/2)

EPICS

Time – Eastern Time (US)	Topic	Speaker/Moderator
5.00 PM – 5.05 PM (5 min)	Welcome and Introductions	Corey J. Langer, MD, FACP
5.05 PM – 5.25 PM (20 min)	Prognostic and Predictive Biomarkers in NSCLC – Clinical vs Research Relevance (excluding *EGFR/ALK*)	Ignacio Wistuba, MD
5.25 PM – 5.55 PM (30 min)	Discussion – Prognostic and Predictive Biomarkers in NSCLC – Clinical vs Research Relevance (excluding *EGFR/ALK*)	Moderator: Corey J. Langer, MD, FACP
5.55 PM – 6.10 PM (15 min)	New Directions for *EGFR*-Mutant NSCLC	Antoinette Wozniak, MD, FACP, FASCO
6.10 PM – 6.30 PM (20 min)	Discussion – New Directions for *EGFR*-Mutant NSCLC	Moderator: Corey J. Langer, MD, FACP
6.30 PM – 6.40 PM (10 min)	Emergence of Immunotherapy and Bispecifics in SCLC	Antoinette Wozniak, MD, FACP, FASCO
6.40 PM – 6.50 PM (10 min)	Discussion – Emergence of Immunotherapy and Bispecifics in SCLC	Moderator: Corey J. Langer, MD, FACP
6.50 AM – 7.00 PM (10 min)	BREAK	

Meeting Agenda – Day 1 (2/2)

EPICS

Time – Eastern Time (US)	Topic	Speaker/Moderator
7.00 PM – 7.15 PM (15 min)	Therapeutic Landscape for Fusion-Positive NSCLC (*ALK, ROS1, NTRK, RET*)	Karen Reckamp, MD, MS
7.15 PM – 7.45 PM (30 min)	Discussion – Therapeutic Landscape for Fusion-Positive NSCLC (*ALK, ROS1, NTRK, RET*)	Moderator: Corey J. Langer, MD, FACP
7.45 PM – 8.00 PM (15 min)	Inhibiting Oncogenic Mutations: Overcoming Mutant *KRAS, HER2, MET*, and *BRAF*	David Spigel, MD
8.00 PM – 8.30 PM (30 min)	Discussion – Inhibiting Oncogenic Mutations: Overcoming Mutant *KRAS, HER2, MET*, and *BRAF*	Moderator: Corey J. Langer, MD, FACP
8.30 PM – 8.40 PM (10 min)	New Directions for Second-Line Therapy	Edward Garon, MD
8.40 PM – 9.00 PM (20 min)	Discussion – New Directions for Second-Line Therapy	Moderator: Corey J. Langer, MD, FACP
	Adjourn	Corey J. Langer, MD, FACP

Meeting Agenda – Day 2 (1/2)

EPICS

Time – Eastern Time (US)	Topic	Speaker/Moderator
9.00 AM – 9.05 AM (5 min)	Welcome and Introductions	Corey J. Langer, MD, FACP
9.05 AM – 9.20 AM (15 min)	Perioperative Immunotherapy in Early NSCLC	Karen Reckamp, MD, MS
9.20 AM – 9.50 AM (30 min)	Discussion – Perioperative Immunotherapy in Early NSCLC	Moderator: Corey J. Langer, MD, FACP
9.50 AM – 10.00 AM (10 min)	Immunotherapy in Unresectable Stage III NSCLC	Nasser Hanna, MD
10.00 AM – 10.20 AM (20 min)	Discussion – Immunotherapy in Unresectable Stage III NSCLC	Moderator: Corey J. Langer, MD, FACP
10.20 AM – 10.35 AM (15 min)	First-Line Immunotherapy in Metastatic NSCLC – Single Agent or Combination?	Roy Herbst, MD, PhD
10.35 AM – 11.05 AM (30 min)	Discussion – First-Line Immunotherapy in Metastatic NSCLC: Single Agent or Combination?	Moderator: Corey J. Langer, MD, FACP
11.05 AM – 11.15 AM (10 min)	BREAK	

Meeting Agenda – Day 2 (2/2)

EPICS

Time – Eastern Time (US)	Topic	Speaker/Moderator
11.15 AM – 11.30 AM (15 min)	Biomarkers for Immunotherapy – Making Sense of the Chaos	Roy Herbst, MD, PhD
11.30 AM – 11.50 AM (20 min)	Discussion – Biomarkers for Immunotherapy – Making Sense of the Chaos	Moderator: Corey J. Langer, MD, FACP
11.50 AM – 12.00 PM (10 min)	*EGFR* (Less Common Mutations, Including Exon 20 Insertions)	Natasha Leighl, MD, MMSc, FRCPC, FASCO
12.00 PM – 12.10 PM (25 min)	Discussion – *EGFR* (Less Common Mutations, Including Exon 20 Insertions)	Moderator: Corey J. Langer, MD, FACP
12.10 PM – 12.20 PM (10 min)	Promising New Targets/Agents in Lung Cancer	David Spigel, MD
12.20 PM – 12.40 PM (20 min)	Discussion – Promising New Targets/Agents in Lung Cancer	Moderator: Corey J. Langer, MD, FACP
	Conclusions and Adjourn	Corey J. Langer, MD, FACP

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Summaries of Faculty Presentations

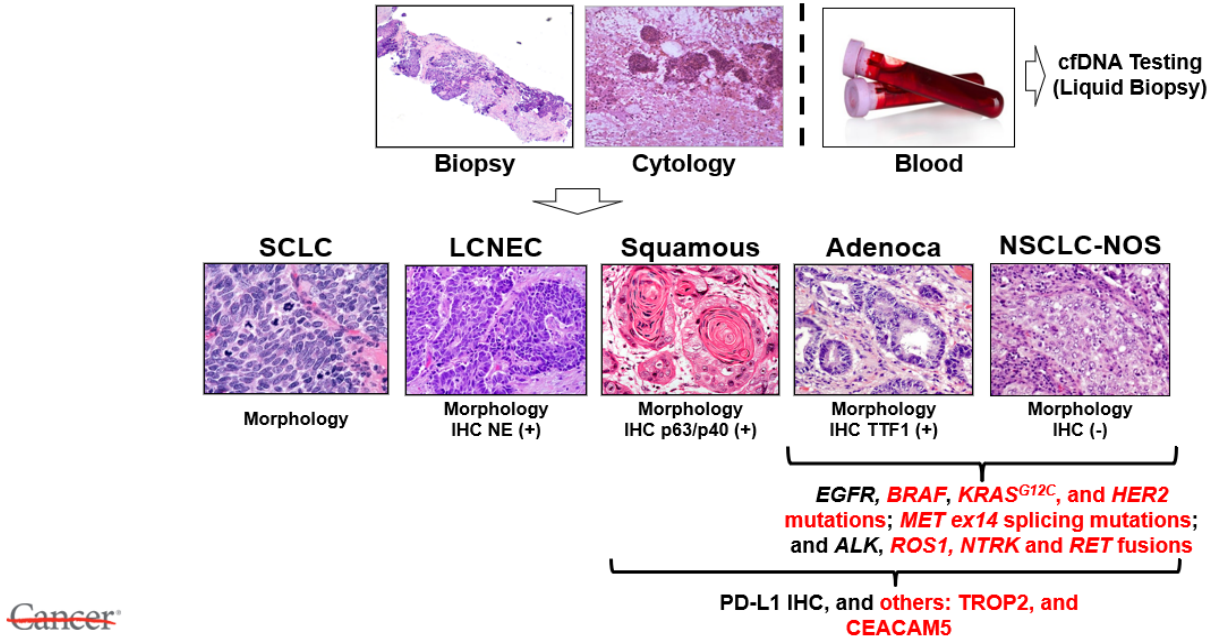
Prognostic and Predictive Biomarkers in NSCLC (1/2)

Presented by Ignacio Wistuba, MD

EPICS

- The importance of molecular testing in metastatic NSCLC, including evaluation for PD-L1 expression and oncogenic drivers, has been established over the past 1 to 2 decades
  - With the approval of targeted therapy and immunotherapy in earlier disease settings, molecular testing in lung cancer continues to expand
  - The list of molecular markers continues to increase, and emerging concepts include surrogate markers of survival with perioperative immunotherapy, such as major/complete pathologic response and measurable residual disease

Diagnostic Algorithm for Lung Cancer Diagnosis 2021



Cancer

Prognostic and Predictive Biomarkers in NSCLC (2/2)

Presented by Ignacio Wistuba, MD

EPICS

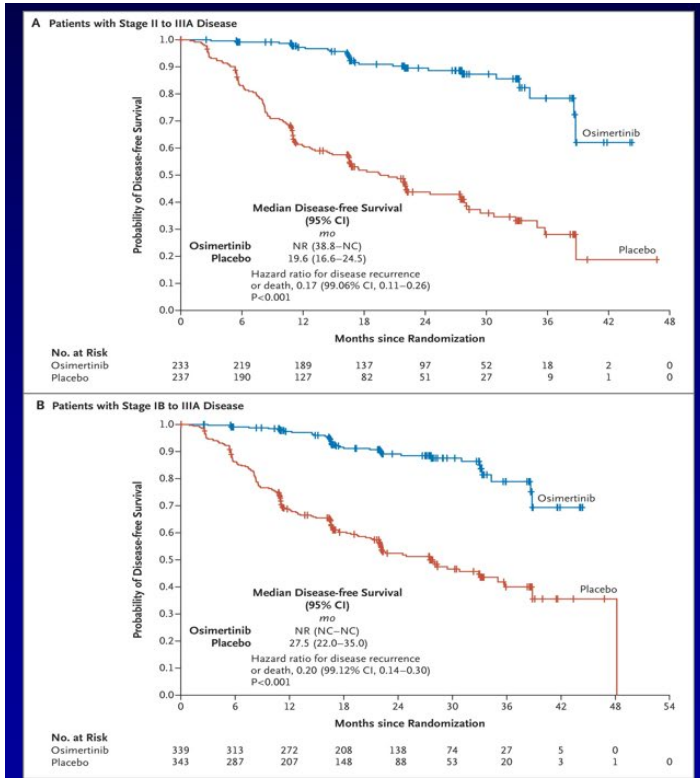
- Equally important paradigm evolutions in molecular testing revolve around technical aspects of molecular testing
  - Tissue vs liquid biopsy
    - Tissue-based testing allows for assessment of both DNA and non-DNA biomarkers, as well as histology and PD-L1; however, this method is more invasive and requires a longer turnaround time
    - Liquid-based testing is minimally invasive, provides a short turnaround time, and can capture tumor heterogeneity, but may result in false negatives, particularly in patients with low tumor burden (ie, low ctDNA shedding)
  - NGS vs more limited (eg, PCR) testing platforms
    - NGS-based testing conserves tissue and allows for detection of a wide range of molecular abnormalities, which allows the potential for access to approved and experimental targeted agents, but requires a longer turnaround time compared with other approaches
    - PCR-based testing results can be received rapidly, although not all mutations and variations may be detected, as these approaches are biased toward hotspot mutations

New Directions for *EGFR*-Mutant NSCLC (1/2)

Presented by Antoinette Wozniak, MD, FACP, FASCO

EPICS

- The most significant advance in the management of *EGFR* mutation-positive NSCLC is the December 2020 approval of osimertinib as adjuvant therapy, on the basis of the phase III ADAURA trial that demonstrated improved DFS of osimertinib compared with placebo
- In patients with metastatic NSCLC and a common *EGFR* mutation (exon 19 or 21), single-agent osimertinib remains the preferred approach



ADAURA: Adjuvant Osimertinib

- Phase III – Stages IB-IIIA resected EGFR+ pts randomized to receive Osimertinib v placebo for 3 yr
- Adjuvant chemotherapy was allowed
- mDFS was significantly longer for Osimertinib HR = 0.17
  - IB, HR 0.50
  - II, HR 0.17
  - IIIA HR 0.12
- FDA approved 12/18/20

Wu Y-L, et al, NEJM 383:1711, 2020

New Directions for *EGFR*-Mutant NSCLC (2/2)

Presented by Antoinette Wozniak, MD, FACP, FASCO

EPICS

- Key areas of investigation include improving the efficacy of first-line therapy, and evaluating novel agents post-osimertinib
  - Improving first-line therapy: Combinations of first-generation EGFR TKIs with antiangiogenic agents have demonstrated improved PFS compared with the TKI alone, although an OS benefit has not yet been demonstrated. Trials are ongoing to evaluate the addition of bevacizumab (EA5182) or ramucirumab (LUN18-335) to osimertinib. Additionally, trials such are FLAURA2 are ongoing to evaluate the addition of platinum-based chemotherapy to osimertinib as initial therapy in patients with *EGFR* mutation-positive NSCLC
  - Post-osimertinib therapy
    - Amivantamab, a bispecific anti-EGFR/MET antibody, has been combined with lazertinib, a third-generation EGFR TKI, and showed efficacy in patients whose disease progressed on osimertinib (Bauml et al. ASCO 2021, #9006)
    - The anti-HER3 antibody-drug conjugate patritumab deruxtecan demonstrated activity in patients with NSCLC and resistance to an EGFR inhibitor (~90% with prior osimertinib) (Janne et al. ASCO 2021, #9007)

EGFR (Less Common Mutations, Including Exon 20 Insertions) (1/2)

Presented by Natasha Leighl, MD, MMSc, FRCPC, FASCO

EPICS

- *EGFR* exon 20 insertions represent 4% to 12% of *EGFR* mutations
  - Patients with *EGFR* exon 20 insertions represent a significant medical need, due to reduced sensitivity to “classical” EGFR TKIs
  - Exon 20 insertions are numerous and heterogeneous
  - NGS-based testing is important, as PCR-based methods have been shown to miss approximately 50% of the variants identified through NGS
- Platinum-based chemotherapy remains the recommended first-line approach

- Patients with EGFR exon20ins are a population with significant unmet needs
- NGS identifies twice as many insertions as PCR – should be gold standard

- Approval of promising new second-line options amivantamab and mobocertinib
- Multiple other agents (predominantly TKIs) in development

- Remaining questions:
  - How best to move to first-line?
  - Should we be moving earlier?
  - Optimal sequencing? Combinations?
  - How to better select patients for each approach (e.g. mutation location)

EGFR (Less Common Mutations, Including Exon 20 Insertions) (2/2)

Presented by Natasha Leighl, MD, MMSc, FRCPC, FASCO

EPICS

- In 2021, 2 agents were approved as subsequent therapy specifically for patients with *EGFR* exon 20 insertions
  - Amivantamab, a bispecific EGFR/MET antibody
  - Mobocertinib, a TKI
  - Without direct comparisons, the choice between the 2 agents is largely determined by the adverse event profile and logistic considerations
    - Amivantamab is associated with infusion reactions in early doses and requires biweekly visits to the clinic for infusions; the initial loading cycle requires weekly dosing, and the first dose is split between day 1 and day 2
    - Mobocertinib is orally available, but grade ≥3 diarrhea was reported in 21% of patients. Other adverse events to be considered are rash and cardiac toxicity (black box warning for QTc prolongation and torsades de pointes)
- Both amivantamab and mobocertinib are being investigated in the first-line setting
- Other TKIs are being investigated for patients with *EGFR* exon 20 insertions, including BDTX-189, CLN-081, DZD9008, furmonertinib, high-dose osimertinib, and poziotinib

Therapeutic Landscape for Fusion-Positive NSCLC (*ALK, ROS1, NTRK, RET*) (1/2)

Presented by Karen Reckamp, MD, MS

EPICS

- A key consideration for oncogenic fusions is the inclusion of RNA-based testing, as DNA-based platforms may miss certain fusions, eg, when the rearrangement occurs in an intron that is too long for effective amplification by DNA-based PCR
- There are currently 4 clinically relevant oncogenic fusions mentioned in NCCN guidelines for NSCLC (version 1.2022); for each fusion, at least 2 targeted agents are recommended
  - *ALK* (alectinib, brigatinib, lorlatinib)
  - *ROS1* (entrectinib, crizotinib)
  - *NTRK* (larotrectinib, entrectinib)
  - *RET* (selpercatinib, pralsetinib)

Methods for Fusion Detection: Targeted RNA sequencing can complement DNA-based NGS by increasing oncogenic fusion detection

	IHC	FISH	DNA NGS	RNA NGS
Pros	✓ Potential local implementation	✓ Potential local implementation	✓ Simultaneously get mutation information	✓ Obtain fusion partner information without intron coverage issues; directly assess fusion expression
Cons	– Significant false neg, pos	– Significant false neg, pos	– Poor coverage of some intronic areas due to repetitive sequences leads to reduced sensitivity	
Consider using?	NOT RECOMMENDED	NOT RECOMMENDED	RECOMMENDED	RECOMMENDED

Cedars Sinai

Ferrara. J Thorac Oncol. 2018;13:27.

Therapeutic Landscape for Fusion-Positive NSCLC (*ALK, ROS1, NTRK, RET*) (2/2)

Presented by Karen Reckamp, MD, MS

EPICS

- *NRG1* represents an emerging class of oncogenic fusions, with a frequency of 0.3% in NSCLC (Jonna et al. *Clin Cancer Res*. 2019;25:4966)
  - Currently, there is no targeted agent approved for *NRG1* fusions. Given the interaction between *NRG1* fusions and HER3, antibodies targeting HER3 are currently under investigation, including seribantumab (NCT04383210) and zenocutuzumab (NCT02912949)

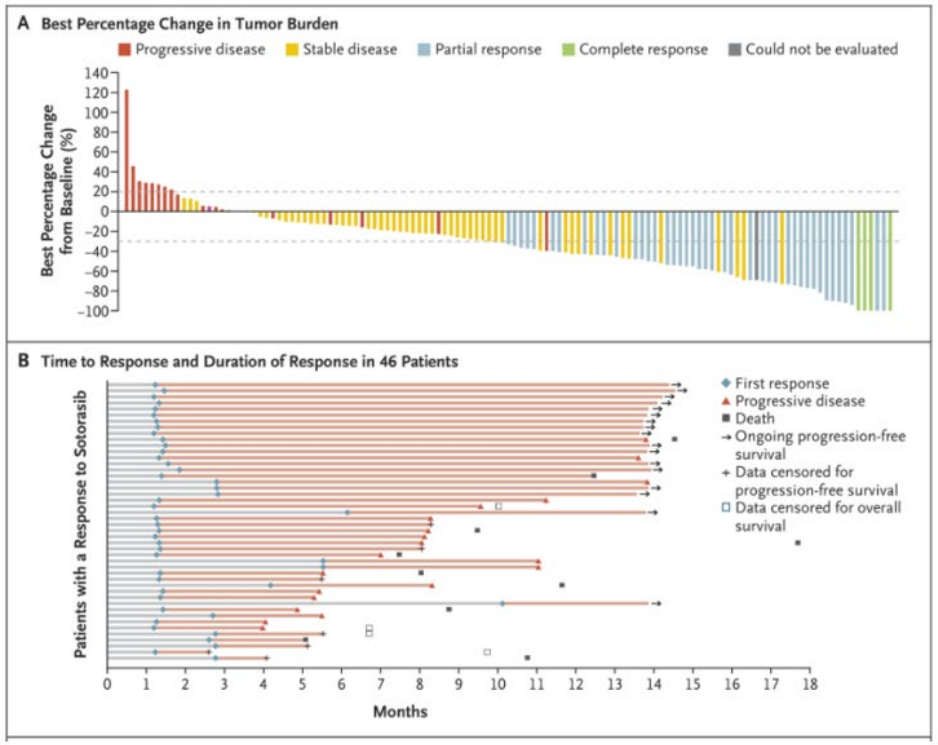
Inhibiting Oncogenic Mutations: Overcoming Mutant *KRAS, HER2, MET,* and *BRAF* (1/2)

Presented by David Spigel, MD

EPICS

- The most recent development in actionable mutations in lung cancer is the long-awaited approval of a targeted agent for patients with a *KRAS* mutation, with the May 2021 accelerated approval of sotorasib for *KRAS* G12C-positive NSCLC following at least 1 prior systemic therapy

Sotorasib



Skoulidis, NEJM 2021

Inhibiting Oncogenic Mutations: Overcoming Mutant *KRAS, HER2, MET,* and *BRAF* (2/2)

Presented by David Spigel, MD

EPICS

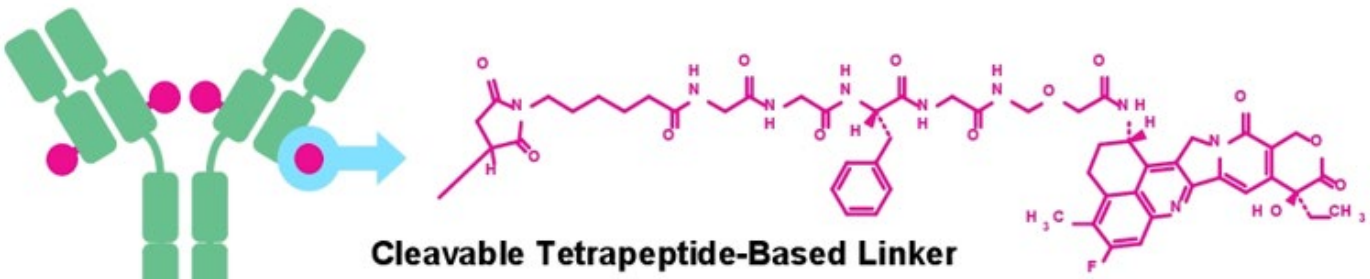
- For *HER2*, *MET*, and *BRAF*, targeted agents have either been approved or have demonstrated promising activity and are listed in NCCN guidelines for NSCLC (version 1.2022)
  - *KRAS* (sotorasib)
    - Other agents are under investigation for *KRAS*-mutated NSCLC, including adagrasib and pan-KRAS inhibitors
  - *HER2* (currently no approved agents; trastuzumab emtansine and trastuzumab deruxtecan are mentioned in NCCN guidelines
    - TKIs, such as poziotinib, are also in development for patients with *HER2* mutations
  - *MET* exon 14 skipping mutation (capmatinib, tepotinib)
    - Other agents under investigation include amivantamab (*MET* exon 14) and telisotuzumab vedotin (*MET* expression)
  - *BRAF* (dabrafenib + trametinib)

Promising New Targets/Agents in Lung Cancer

Presented by David Spigel, MD

EPICS

- Antibody-drug conjugates (ADCs) have been approved in hematologic malignancies, breast cancer, and bladder cancer, and this class of agents is also being investigated in lung cancer
  - ADCs directed toward HER2 have been discussed in the oncogenic mutations section
  - Additional targets for ADCs not associated with oncogenic drivers include TROP-2, CEACAM5, and B7-H3
- Cell-based therapy is also under investigation in lung cancer, with early studies focusing on mesothelin-expressing tumors



Perioperative Immunotherapy in Early NSCLC

Presented by Karen Reckamp, MD, MS

EPICS

- The use of immunotherapy in patients with resectable disease represents one of the major advances in lung cancer, with adjuvant atezolizumab receiving FDA approval in October 2021 for patients with stage II–IIIA NSCLC and PD-L1 expression level ≥1% following surgery and adjuvant chemotherapy
  - Approval of atezolizumab was based on the phase III IMpower010 study, in which atezolizumab improved DFS compared with best supportive care in patients with stage II–IIIA NSCLC and PD-L1 expression ≥1% (HR, 0.66; 95% CI 0.50-0.88; *P* = .0039)
  - In the phase III CheckMate 816 study, the addition of nivolumab to neoadjuvant chemotherapy increased the pCR rate compared with chemotherapy alone (24% vs 2%; OR, 13.94; *P* <.0001); this study also met the EFS endpoint
  - There remain several questions, including if surrogate endpoints, such as MPR, PCR, or DFS/EFS can be used in place of OS

Advances in Early-Stage NSCLC: Conclusions

- Immune checkpoint inhibitors and targeted therapies are now being moved earlier in the disease course of NSCLC
- IMpower010 established that adjuvant atezolizumab prolongs DFS in patients with stage II-III NSCLC
  - Benefit is most concentrated in PD-L1 ≥1%, in particular PD-L1 ≥50%

Press release 11/8/2021
…the Phase 3 CheckMate -816 trial met the primary endpoint of improved event-free survival (EFS) in patients with resectable stage IB to IIIA non-small cell lung cancer (NSCLC). In a prespecified interim analysis, nivolumab plus chemotherapy showed a statistically significant and clinically meaningful improvement in EFS compared to chemotherapy alone when given before surgery.

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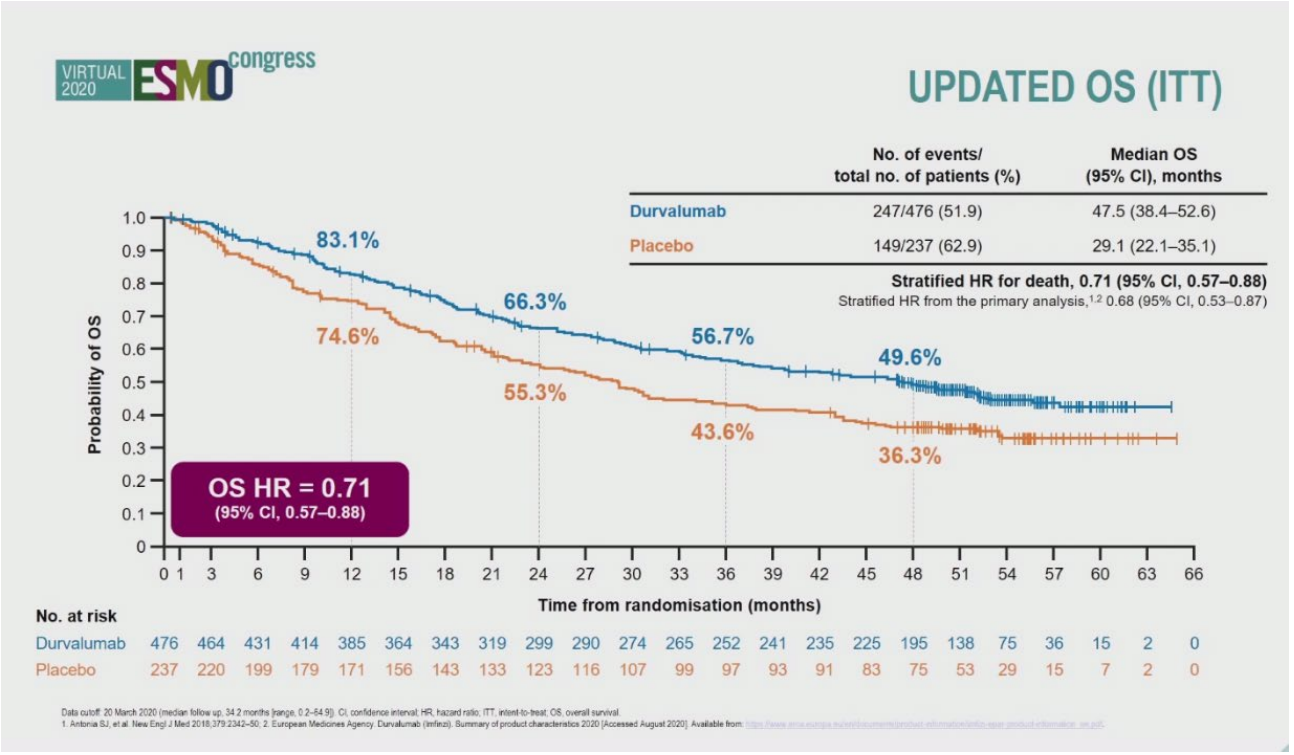
Immunotherapy in Unresectable Stage III NSCLC

Presented by Nasser Hanna, MD

EPICS

- The phase III PACIFIC trial continues to define the standard of care for patients with unresectable stage III NSCLC with consolidation durvalumab yielding superior PFS and OS compared with placebo in patients who achieved a response or stable disease after chemoradiation therapy (CRT)
  - The 5-year update presented in 2021 showed continued superior efficacy with durvalumab in terms of PFS (33% vs 19%) and OS (43% vs 33%)
- Efforts to build on the PACIFIC trial include the administration of immunotherapy during CRT (eg, PACIFIC2, KEYLYNK-012), and immunotherapy-based combinations during consolidation (eg, COAST)



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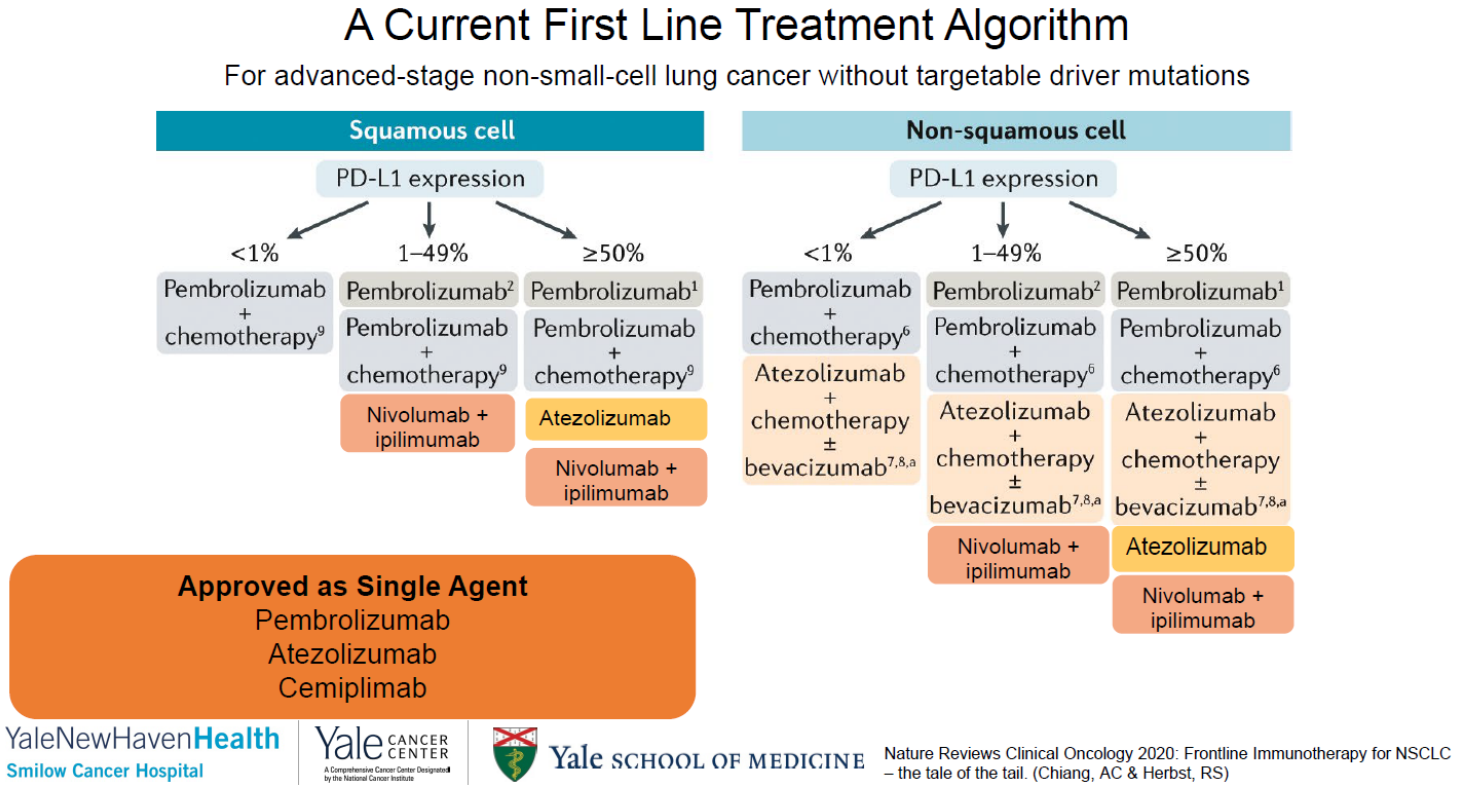
First-Line Immunotherapy in Metastatic NSCLC – Single Agent or Combination? (1/2)

Presented by Roy Herbst, MD, PhD

EPICS

- There are currently multiple options for first-line therapy of patients with metastatic NSCLC and no actionable oncogenic drivers; PD-L1 expression is a key determinant
  - <1%: chemotherapy +/- immunotherapy
  - 1% to 49%: immunotherapy +/- chemotherapy (single-agent immunotherapy in selected patients); immunotherapy doublet
  - ≥50%: immunotherapy +/- chemotherapy; immunotherapy doublet



YaleNewHavenHealth Smilow Cancer Hospital | Yale CANCER CENTER | Yale SCHOOL OF MEDICINE

Nature Reviews Clinical Oncology 2020: Frontline Immunotherapy for NSCLC – the tale of the tail. (Chiang, AC & Herbst, RS)

First-Line Immunotherapy in Metastatic NSCLC – Single Agent or Combination? (2/2)

Presented by Roy Herbst, MD, PhD

EPICS

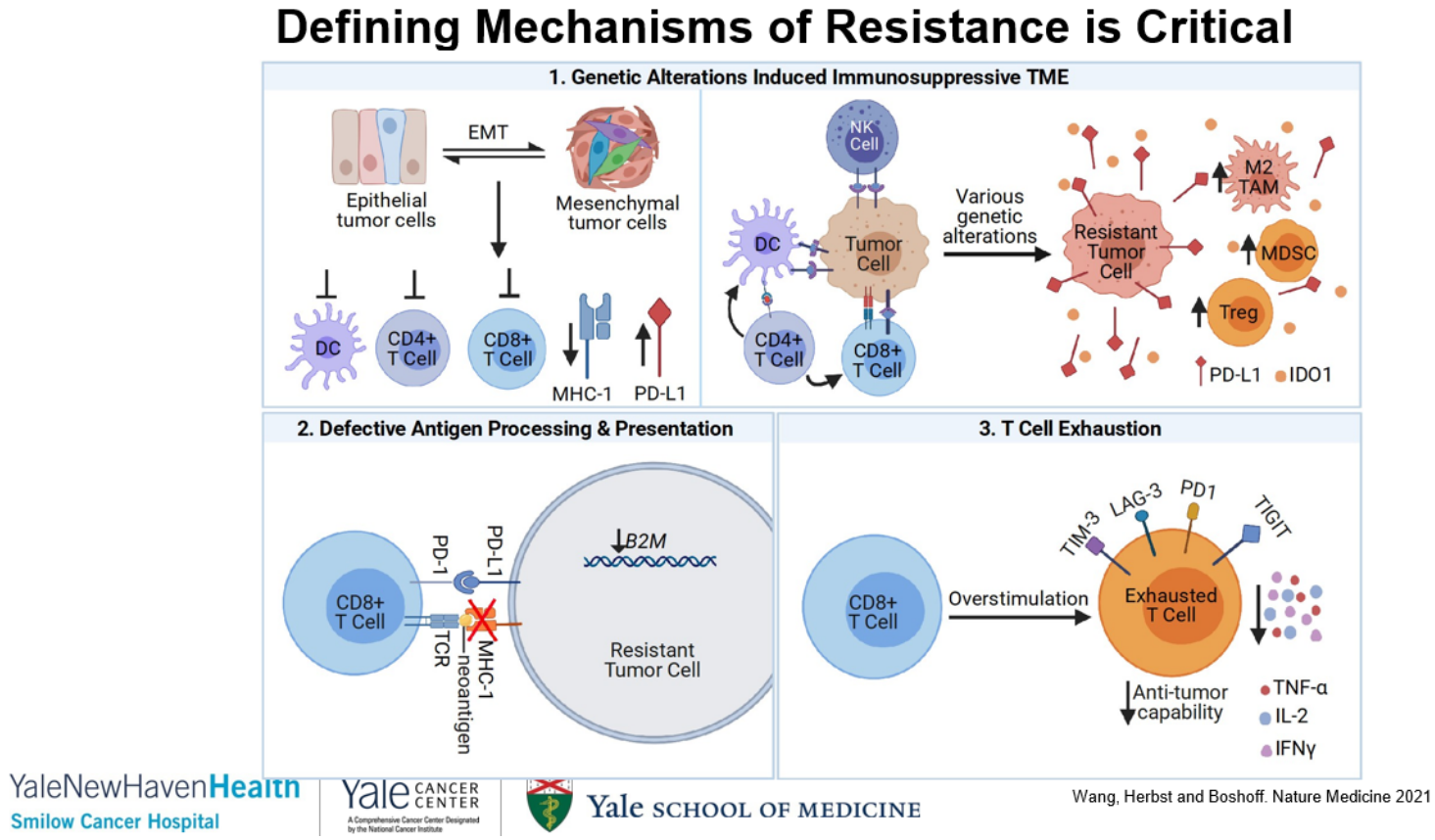
- Data presented in 2021 reinforced the concept that immunotherapy benefits patients with brain metastases (ATEZO-BRAIN), and that combined blockade of PD-L1 and CTLA-4 can extend the efficacy of chemotherapy (POSEIDON)
- Ongoing questions in the first-line setting include the timing of platinum-based chemotherapy in patients with PD-L1–positive disease (ie, upfront in combination with immunotherapy, or in the second-line setting), which is currently being addressed in the phase III INSIGNA trial
- Investigational approaches to improve outcomes of first-line chemotherapy include combinations of immunotherapy and multikinase inhibitors (eg, LEAP-006 trial) and new immunotherapeutic targets such as TIGIT (SKYSCRAPER-01 study)

Biomarkers for Immunotherapy – Making Sense of the Chaos

Presented by Roy Herbst, MD, PhD

EPICS

- PD-L1 is still the main biomarker for immunotherapy despite its shortcomings
- Markers such as TMB, *STK11*, and *KRAS* mutations remain investigational
- Additional avenues of investigation revolve around the tumor microenvironment, particularly the observation that many lung tumors are immunologically “cold” with little or no penetration by tumor-infiltrating lymphocytes
- Mechanisms of resistance to therapy are being defined, with the goal of identifying therapeutic approaches
  - Genetic alterations leading to an immunosuppressive microenvironment
  - Defective antigen processing/ presentation due to loss of beta-2-microglobulin and MHC-1 function
  - Exhaustion of CD8-positive T cells



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Wang, Herbst and Boshoff. Nature Medicine 2021

New Directions for Second-Line Therapy

Presented by Edward Garon, MD

EPICS

- Treatment of patients with advanced NSCLC after progression on immunotherapy + chemotherapy remains a major unmet need in 2022
- Docetaxel +/– ramucirumab are still the main approved options
- The phase III DUBLIN-3 study compared the combination of plinabulin + docetaxel with placebo + docetaxel in patients with platinum-pretreated NSCLC; however, few patients in this study had received prior immunotherapy, potentially limiting the application to current clinical realities
- Single-arm trials combining immunotherapy with a multikinase inhibitor have demonstrated encouraging response in immunotherapy-pretreated patients; however, randomized trials are still needed to determine the efficacy of this approach

- **Best results are with docetaxel plus anti-angiogenic therapy, but single agent docetaxel is regulatory control**
- **Plinabulin has positive but odd data**
- **PD-1 inhibition plus multi-targeted tyrosine kinase inhibition has impressive data, but no randomized data to date**

UCLA

Emergence of Immunotherapy and Bispecifics in SCLC

Presented by Antoinette Wozniak, MD, FACP, FASCO

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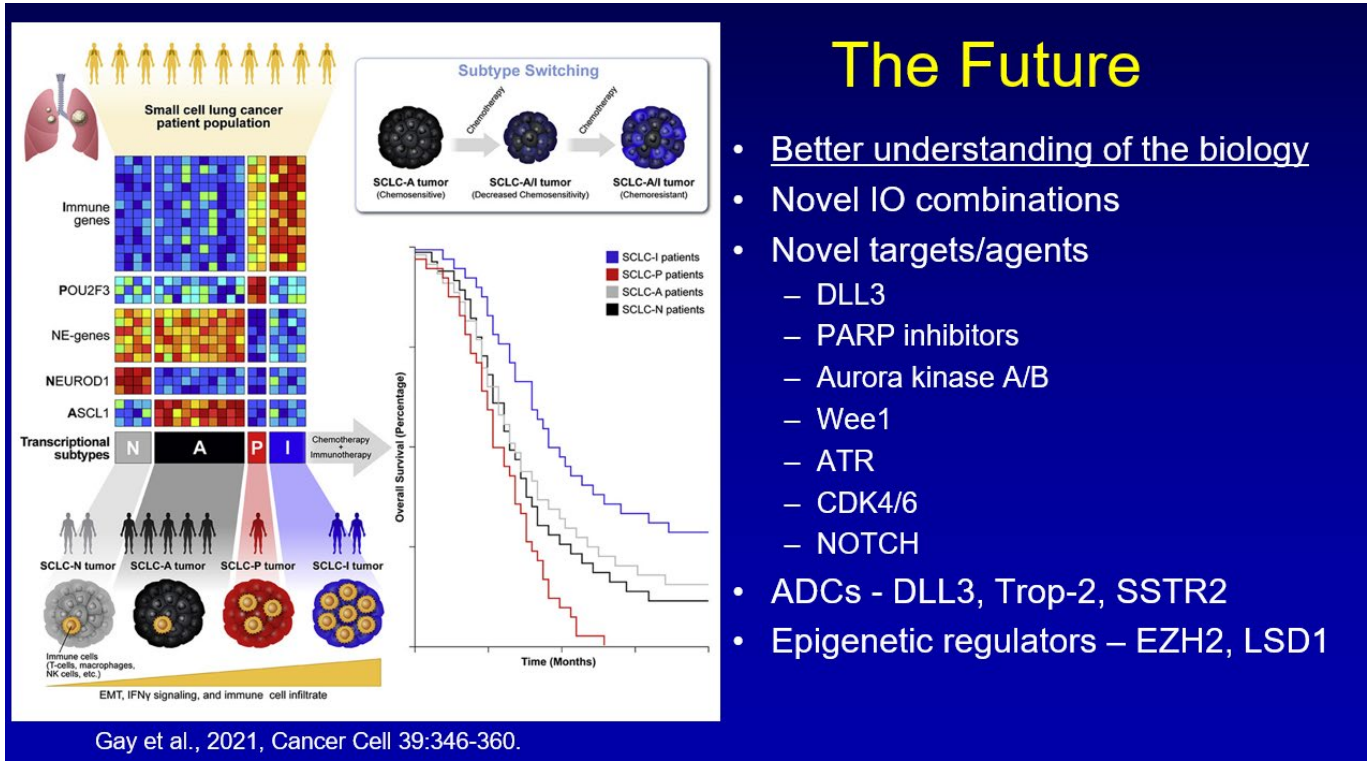
- After several decades with little progress, a new first-line standard of care for patients with ES-SCLC was established in 2019/2020 with the approvals of atezolizumab-carboplatin-etoposide and durvalumab-platinum-etoposide on the basis of the IMpower133 and CASPIAN trials, respectively
- Relapsed/refractory SCLC remains a challenging disease to manage
  - Lurbinectedin monotherapy received accelerated approval in 2020 for patients with platinum-pretreated SCLC. The subsequent ATLANTIS trial, comparing lurbinectedin-doxorubicin with topotecan or CAV, did not meet the primary endpoint of OS, although the experimental arm added doxorubicin. The phase III confirmatory LAGOON trial is in progress, and will compare single-agent lurbinectedin with lurbinectedin + irinotecan or single-agent irinotecan or topotecan
  - Several early phase trials are in progress to evaluate other potential therapeutic targets, such as DLL3 and DNA damage repair



Gay et al., 2021, Cancer Cell 39:346-360.

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Key Insights

Prognostic and Predictive Biomarkers in NSCLC (1/2)

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The experts would use liquid-based testing primarily for patients who were diagnosed outside their institution and/or if there is concern about insufficient tissue; however, they did not indicate reflexive use of liquid biopsies

- The experts estimated that overall (internally diagnosed or referred from outside), 5% to 10% of their patients had insufficient tissue – the fact that most patients had sufficient tissue was credited in large part to improved procedures in the oncology community, although internal biopsy procedures have improved as well
- One of the experts mentioned that patients diagnosed using Ion bronchoscopy tended to have smaller specimens and were more likely to have issues with tissue insufficiency
- For liquid-based testing, most of the experts indicated their institution uses the Guardant panel, with 1 expert each using the panel from Tempus or Foundation Medicine

Expert opinion is that RNA-based testing is necessary to detect oncogenic fusions, and they reported using both DNA- and RNA-based testing in newly diagnosed patients

- While RNA-based testing is preferred, the pathology expert stated that DNA-based assays can be considered if the panel contains the most frequent fusion partners (where applicable)

Rapid immunohistochemistry tests for *EGFR, ALK*, and *ROS1* are used by the experts in parallel with NGS-based testing

The pathology expert stated that multigene panels generally detect *EGFR* exon 20 insertions; nevertheless, there were some concerns that some variants might be missed

> ***Dr Wistuba:***
> *To target the fusions, you need to target the gene of interest and the partner. When you use hybrid capture NGS . . . you have more opportunity to be more comprehensive, but you still need to know the genes that are partners. The best way to deal with this is to do RNA-based approach . . .*

Prognostic and Predictive Biomarkers in NSCLC (2/2)

EPICS

Expert opinion is that *MET* amplification is an actionable marker, and capmatinib and tepotinib are both active in this setting

The approach to comprehensive molecular testing in patients with squamous histology varies among the experts; however, comprehensive testing generally would not be done for a patient with a heavy smoking history

- Particularly on the West coast, patients with a never-smoking or light-smoking history would be considered for comprehensive testing regardless of histology
- One of the experts indicated their institution has done comprehensive testing on all lung cancer patients since 2012

Expert opinion is that for ADCs that are not currently associated with target-specific selection (eg, TROP2, HER3), studies should take all comers, then assess response by expression of the target

New Directions for *EGFR*-Mutant NSCLC (1/2)

EPICS

Molecular testing of patients with early stage NSCLC varied, ranging from *EGFR* only (n = 1), to *EGFR* and *ALK* (n = 1) and NGS-based testing (n = 2)

Regarding the use of adjuvant osimertinib as studied in the ADAURA trial, the experts generally agreed that the data on brain metastases are convincing enough to offer this therapy to patients with resected, *EGFR* mutation-positive NSCLC

- However, the experts do not extrapolate the ADAURA data in stage IB–IIIA NSCLC to patients with stage IA disease or unresectable stage III disease. For the latter setting, the negative OS results with an EGFR TKI in the S0023 study are still relevant to the experts
- Additionally, there are concerns that adjuvant TKI therapy is not actually curative, given that OS data from ADAURA are not currently available and previous studies demonstrated improved PFS but not OS
- Nevertheless, the HR for DFS was extremely favorable for osimertinib, and experts described that patients always want to receive adjuvant osimertinib after discussing treatment options
- Even if there is no OS benefit with adjuvant osimertinib, expert opinion is that avoiding the psychological difficulties of disease relapse is worthwhile

None of the experts reported having patients who have progressed on adjuvant osimertinib (one of the experts confirmed having patients who are receiving osimertinib as adjuvant therapy)

- In terms of managing patients who progress, the planned approach is to rechallenge with osimertinib for patients who have been off therapy for at least 3 months; if a patient progresses during adjuvant osimertinib, the plan would be to request molecular testing (both liquid and tissue based) to search for actionable resistance mechanisms, and to assess the pattern of progression (local vs diffuse)

> ***Dr Spigel:***
> *I'm not sure you're probably curing anybody [with adjuvant osimertinib]. I think you're pushing things off. [But] when the ESMO CNS data came out . . . I thought that was good enough for me . . .*

New Directions for *EGFR*-Mutant NSCLC (2/2)

EPICS

In the metastatic setting, the experts generally administer carboplatin-pemetrexed to patients who have disease that is refractory to osimertinib

- Four of the experts continue osimertinib
- Two would continue osimertinib only if the patient had brain metastases
- Additionally, 2 of the experts also use bevacizumab
- In terms of molecular testing to search for targetable mechanisms of resistance, there are concerns from the experts that testing only tissue or only blood would risk missing a potential therapeutic target

EGFR (Less Common Mutations, Including Exon 20 Insertions)

EPICS

For patients with an *EGFR* exon 20 insertion, the experts would recommend chemotherapy without immunotherapy in the frontline setting

In subsequent lines of therapy, one of the experts reported seeing benefit using amivantamab and mobocertinib sequentially, in either order

However, the experts think both amivantamab and mobocertinib are challenging drugs, which would have implications on long-term therapy

> Amivantamab is associated with frequent infusions initially, along with infusion reactions
> Mobocertinib is associated with severe diarrhea that in some cases does not respond to dose reduction

Regarding the EXCLAIM-2 study comparing mobocertinib with chemotherapy as initial therapy in patients with NSCLC and an *EGFR* exon 20 insertion, one of the experts related that the trial was reopened and had passed the futility analysis; however, there is still doubt as to whether mobocertinib would ultimately be able to demonstrate superiority over chemotherapy

> ***Dr Leighl:***
> *We've gone from mobocertinib to amivantamab and seen benefit, and vice versa. So again, we need to understand more about why patients respond to different treatments and what some of these biomarkers are that we can use.*

Therapeutic Landscape for Fusion-Positive NSCLC (*ALK, ROS1, NTRK, RET*)

EPICS

Expert opinion is that more education is needed to ensure that all appropriate patients have access to molecular testing for oncogenic fusions; one of the experts mentioned that many patients are referred having received only single-gene testing

For oncogenic fusions with currently approved agents (*ALK, ROS1, NTRK, RET*), expert opinion is that the TKIs are the first-line therapy of choice

For initial therapy of patients with *ALK*-rearranged NSCLC, 6 of the experts used alectinib (n = 5) or brigatinib (n = 2); this includes 1 expert who uses either agent in the frontline setting

> Expert opinion is that ALK TKIs clearly prevent CNS metastases, on the basis of data from ALEX (alectinib), ALTA-1L (brigatinib), and CROWN (lorlatinib) trials
> Lorlatinib is viewed as more challenging due to toxicity, so experts reserve this agent for subsequent lines of therapy; however, the CNS activity of lorlatinib is viewed favorably

Regarding patients with *ROS1*-rearranged NSCLC, there was a slight preference for entrectinib (n = 3) over crizotinib (n = 2)

> The activity of entrectinib in the CNS would lead experts to use this agent preferentially in patients with brain metastases
> There is some concern over toxicity, including neurocognitive effects, with entrectinib, which has led one of the experts to generally prefer crizotinib

In patients with NSCLC and an oncogenic fusion whose disease becomes TKI refractory, the experts approach this in a manner similar to that of *EGFR* mutation-positive NSCLC, namely chemotherapy

Dr Reckamp:
I think the most important thing is that we need to be testing for [fusions]. I still unfortunately see patients referred to me that get single-gene testing, so they're nowhere near getting RET and NTRK, and if we don't test, we're not going to see these prolonged survivals for patients.

Inhibiting Oncogenic Mutations: Overcoming Mutant *KRAS*, *HER2*, *MET*, and *BRAF* (1/2)

EPICS

Testing results for *KRAS* are seen as an area of educational need for community oncologists

- The experts mentioned that some reports do not provide enough detail on the specific *KRAS* mutations
- Community physicians may not realize that not all *KRAS* mutations are equal, and while academic physicians know the difference between G12C and G12V, this difference of 1 letter (representing a different amino acid) may escape the attention of community oncologists
- If the patient is a smoker, the experts are concerned that community physicians may think their patients are unlikely to have an oncogenic driver, given the experience with *EGFR*; however, *KRAS* mutations are strongly associated with smoking
- Additionally, since sotorasib is approved in the second-line setting (in contrast to most other oncogenic drivers with first-line indications), the experts described the need for community physicians to make sure testing for *KRAS* G12C is carried out and that they remember to review the patient's *KRAS* status when considering second-line therapy

Expert opinion is that in NSCLC with the *KRAS* G12C mutation, the data with sotorasib and adagrasib are similar; it is also thought that these agents will eventually be used as first-line therapy

- Combinations are of interest to the experts, particularly with immunotherapy
- The experts were not aware of any concerns for toxicity when using sotorasib after immunotherapy

Dr Hanna:
KRAS G12C just flows off our tongues, but it doesn't flow off their tongues. It's like G12, is it V? Is it 13? Sometimes the report will tell them and sometimes it won't. . . . I think that there is [a need for] continual education not because they're not smart; it's just there's too much to know.

Inhibiting Oncogenic Mutations: Overcoming Mutant *KRAS, HER2, MET*, and *BRAF* (2/2)

EPICS

In patients with *HER2* mutations, the experts currently would use trastuzumab deruxtecan (T-DXd) in the second-line setting, although this agent is also viewed as having first-line potential

> Pulmonary toxicity with T-DXd is the main concern raised by the experts; no prophylactic approaches are currently established, and it is not known how effective steroids are. Expert opinion is that holding therapy appears to decrease the toxicity; however, there is concern the ILD could negatively affect the feasibility of combinations

For patients with *MET* exon 14 mutations, the experts generally regard capmatinib and tepotinib as similar agents and suitable for first-line use; edema is seen as potentially challenging, but most patients can manage

> Expert opinion is that pricing differences could affect the decision between the capmatinib and tepotinib
> One of the experts mentioned first-line data show high responses, but the long-term outcomes did not strongly support first-line use

Regarding amivantamab, one of the experts with extensive experience with this agent described seeing efficacy in different contexts, including *MET* amplification and *MET* exon 14 mutations, as well as in patients with *MET*-independent resistance to EGFR TKIs

> Immune-related reactions (IRRs) were observed in about 90% of patients with the first infusion and subsided in the second dose. By the third dose, almost no IRRs occurred. Expert opinion is that education of patients and infusion centers will be important regarding the pattern of IRRs

One of the experts discussed experience treating patients with non-V600E mutations of *BRAF*; after finding evidence that the particular mutation was an oncogenic driver, the patients were treated with BRAF/MEK inhibition, with benefit observed

Promising New Targets/Agents in Lung Cancer

EPICS

Antibody-drug conjugates are of interest to the experts

> The enthusiasm for T-DXd has been discussed previously; the responses with datopotamab deruxtecan (Dato-DXd), which targets TROP2, are also considered impressive
> The ADCs are considered by the experts to be targeted chemotherapy, and therefore have the potential to be combined with immune checkpoint inhibitors
> Expert opinion is that there is a need for selective biomarkers with ADCs such as Dato-DXd
> The experts also stated there is a need to establish a strategy to address ADC-related toxicities (eg, pulmonary toxicity with deruxtecan, ocular toxicity with vedotin)

The experts think it would be challenging to establish chimeric antigen receptor (CAR) T cells in advanced lung cancer, as the patient's disease needs to be stable enough during the manufacturing process

> Expert opinion is that evaluating CAR T cells in the adjuvant setting might eliminate this time pressure
> It is also thought that combination with other agents, such as immunotherapy, would be necessary, as the efficacy with CAR T cells alone has been modest

"***Dr Leighl:***
Antibody-drug conjugates, I think we're very excited about them. It's interesting that they sort of each all have their unique toxicities, so there's the deruxtecans and all the pulmonary issues, and then there's the vedotins and eye and other issues . . ."

Perioperative Immunotherapy in Early NSCLC (1/2)

EPICS

The experts discussed the assessment of pathologic complete response (pCR) and major pathologic response (MPR) in patients with NSCLC who have received neoadjuvant immunotherapy

- The pathology expert stated this is not technically difficult, as it is done in other tumor types
- However, there is additional processing and analysis time (eg, processing 10 to 12 slides instead of 3), which may incur additional charges
- Assessment of pCR would require examining the entire tumor, which is not currently done in lung cancer
- Pathologists will also need education on recognizing the tumor bed and areas adjacent to the tumor
- Expert opinion is that the pathologic features of tumors treated with neoadjuvant immunotherapy are not vastly different from those treated with chemotherapy, although there is more inflammation and immune cells

The experts think there are advantages and disadvantages for both adjuvant and neoadjuvant approaches

- Factors favoring the neoadjuvant approach
  - Academic setting
  - Large tumors (larger stage IIIA disease)
  - Potential to downstage tumor, allowing for minimally invasive surgery
  - Ability to directly observe efficacy of the systemic therapy
- Factors favoring the adjuvant approach
  - Adjuvant immunotherapy is already approved, on the basis of IMpower010
  - Less-bulky disease (ie, stage II or stage IIIA disease with occult nodal involvement)
  - In the community, surgery as the initial treatment is the norm; changing this habit will require both the surgeon and patient to wait for surgery, so there would need to be data indicating a strong benefit with the neoadjuvant approach
- It was mentioned that trials of neoadjuvant immunotherapy also have an adjuvant component, so future standards of care may use both approaches

> ***Dr Hanna:***
> *. . . to do neoadjuvant therapy requires a lot of discipline. It means the patient has to be disciplined, it means the surgeon has to be disciplined, and unless you can show a compelling improvement in the neoadjuvant approach, it's going to be hard to convince people to break those patterns. In academia neoadjuvant is much easier to do . . .*

Perioperative Immunotherapy in Early NSCLC (2/2)

EPICS

Expert opinion is that it will be important to develop a management strategy for patients who receive neoadjuvant immunotherapy, but do not achieve a response milestone (eg, pCR)

While an exploratory analysis of IMpower010 suggested that benefit of adjuvant atezolizumab was concentrated in patients with a PD-L1 ≥50%, the experts would still offer therapy according to the indication (≥1%)

- It was mentioned by one of the experts that IMpower010 was not powered to compare PD-L1 ≥50% and 1% to 49% cohorts
- None of the experts have treated a patient with adjuvant atezolizumab since approval, but 2 experts mentioned having patients who are about to begin therapy

Since patients with squamous NSCLC benefited less in IMpower010 than those with nonsquamous histology, expert opinion is that it will be important to observe outcome in patients with squamous histology in upcoming trials, as a histology-dependent approach may be necessary

- Similarly, current smokers had worse DFS compared with former and never smokers in IMpower010, in contrast to what was observed in the metastatic setting, so it will be of interest to see if this is observed in other trials

For patients who progress after adjuvant immunotherapy, the experts speculated that patients who relapse after 6–12 months could be rechallenged with the same chemotherapy regimen with immunotherapy; if relapse happens sooner, then a different cytotoxic regimen would be used with immunotherapy

Immunotherapy in Unresectable Stage III NSCLC

EPICS

The experts generally do not use PD-L1 in deciding whether to offer a patient consolidation immunotherapy after CRT

> Expert opinion is that pretreatment PD-L1 assessment may not reflect the tumor's biology after chemoradiation therapy and is therefore not definitive for this marker. Additionally, the OS and PFS benefit was lower in patients with squamous histology, and there is currently no conversation to exclude squamous NSCLC from consolidation immunotherapy
> Exceptions include a patient who is borderline ineligible for immunotherapy due to comorbidities; a low PD-L1 level might sway the decision to avoid immunotherapy
> Additionally, one of the experts mentioned having a lower threshold to stop immunotherapy for toxicity in patients with PD-L1–negative disease

Four out of 5 the experts would offer consolidation durvalumab to a patient with *EGFR* mutation-positive disease, while 1 expert does not, out of concern for toxicity, particularly ILD, if the patient needs osimertinib subsequently

Expert opinion is that the optimal duration of consolidation durvalumab in stage III NSCLC is not known, and that surrogate biomarkers are needed to tailor therapy, rather than administering immunotherapy for 1 year to all patients

For patients who progress after consolidation durvalumab and who do not have oncogene-driven disease, the experts' approach is to offer standard first-line therapy if it has been at least 6 months, and to recommend second-line options or a clinical trial if <6 months

Regarding the short PFS in the control arm of the COAST trial, expert opinion is that the objective of a randomized, phase II trial is to determine if a phase III trial is justified; in the case of COAST, expert assessment is that the hazard ratios with the addition of oleclumab or monalizumab to consolidation durvalumab clearly justify advancing the combinations to phase III investigation

Dr Reckamp:
I've seen far too many patients who progress on durvalumab and need osimertinib and then have had complications on the osimertinib, mostly interstitial lung disease. I have stopped using durvalumab consolidation in patients with EGFR mutations.

First-Line Immunotherapy in Metastatic NSCLC – Single Agent or Combination? (1/2)

EPICS

The experts were asked about turnaround time for PD-L1 testing; most are able to obtain results within 1 to 2 days

The majority of the patients (at least 90%) whom the experts see would be considered eligible for immunotherapy

> Exceptions include those with baseline idiopathic pulmonary fibrosis and patients who have undergone a liver or heart transplant

For a hypothetical patient with stage IV NSCLC, a 20 pack-year smoking history, PD-L1 expression 60%, and needing treatment but still awaiting molecular testing results, most of the experts would start the patient on chemotherapy alone

> Immunotherapy can be started on the next cycle once it can be confirmed that the patient does not have an oncogenic driver

When asked about the potential of using the CheckMate 9LA regimen (nivolumab-ipilimumab plus 2 cycles of chemotherapy) in PD-L1–negative patients, the experts stated there did not appear to be an efficacy benefit that would justify the toxicity of this regimen

The experts discussed which patients with PD-L1 expression ≥50% they would offer chemotherapy + immunotherapy rather than single-agent immunotherapy

> Symptomatic patients would be offered chemotherapy in addition to immunotherapy
> Although the INSIGNA trial is comparing the 2 approaches, one of the experts mentioned that community physicians prefer to use chemotherapy with immunotherapy even in patients with a PD-L1 expression ≥50%
> One of the experts discussed a patient with autoimmune disease; it is thought the addition of chemotherapy to immunotherapy might decrease autoantibodies

“***Dr Wozniak:***
I think I agree . . . about the patient characteristics, smoker vs nonsmoker, and certainly if the patient was a smoker and sick, I'd probably give the IO-chemotherapy upfront without waiting for the molecular markers. If the patient was a minimal smoker, I probably would give chemotherapy until we got more tumor markers.”

First-Line Immunotherapy in Metastatic NSCLC – Single Agent or Combination? (2/2)

EPICS

Regarding the anti–PD-(L)1 antibodies being developed in China (eg, sintilimab, toripalimab), the experts do not see them as medically distinct from currently available agents; however, the experts would use them if were offered at a lower price

- It was noted that regulatory agencies such as the US Food and Drug Administration do not consider price as part of the review process

The experts discussed emerging immunotherapy targets and approaches of interest

- TIGIT, although the excitement is based on a small, randomized phase II trial, and there is no TIGIT-based biomarker
- The combination of immunotherapy and antiangiogenic agents (eg, LEAP-006 trial) was speculated by one of the experts to have antitumor effects on the microenvironment and antigen presentation
- LAG-3 is also of interest, although on the basis of data in melanoma

Biomarkers for Immunotherapy – Making Sense of the Chaos

EPICS

The experts do not think it is necessary to subdivide the PD-L1 ≥50% population to isolate “very high expressors” (eg, ≥90%)

For a patient with a *KRAS* G12C mutation and high PD-L1 expression, expert opinion is that immunotherapy should be used in the first-line setting, with sotorasib reserved for subsequent therapy

In patients with oncogene-driven NSCLC, the experts agreed PD-L1 status does not affect their decision making

> For drivers associated with nonsmokers (eg, *EGFR, ALK*), immunotherapy would be avoided until the last line of therapy, regardless of PD-L1 expression
> For other drivers (eg, *BRAF, MET, KRAS*), the experts would incorporate immunotherapy earlier, but still after targeted therapy

While not a biomarker per se, expert opinion is that pulmonary function tests, especially DLCO, may be useful to assessing a patient’s suitability for immunotherapy

Expert opinion is that TMB might play at most a minor role as a selective biomarker for immunotherapy

STK11 as a negative predictor for immunotherapy is of interest to the experts

New Directions for Second-Line Therapy

EPICS

Therapy post-chemotherapy/immunotherapy remains the biggest challenge in NSCLC

Docetaxel +/– ramucirumab remains a standard approach, on the basis of the REVEL study; however, expert opinion is that there are few data on this combination following chemotherapy-immunotherapy

Expert opinion is that the data with plinabulin-docetaxel in DUBLIN-3 are not convincing; the company sponsoring the trial highlighted the OS benefit at 4 years with the combination compared with docetaxel alone, but these results were based on only 3 patients

One of the experts mentioned that retreatment with immunotherapy is feasible in some patients, particularly if they previously benefited from immunotherapy; however, it will be necessary to do translational research to evaluate factors, such as MHC, beta-2-microglobulin, and whether a tumor is "hot" or "cold"

> Expert opinion is that rebiopsy will be important, since the pretreatment biopsy may not reflect the biology of relapsed/refractory disease

Results from the MRTX-500 study combining sitravatinib with nivolumab in patients with prior clinical benefit from immunotherapy are seen as promising to the experts, but they cautioned that randomized data will be needed to see if this is a generalizable result, or if these data were simply the result of a highly selected group of patients

The experts support differentiating between patients with relapsed vs primary refractory disease in clinical trials of patients with metastatic disease

There was concern from one of the experts that the changing landscape in patients with *KRAS* mutations may affect the trials, most of which use docetaxel as a control arm

> Patients with *KRAS* mutations were previously shown to have a poor response to docetaxel; however, these patients are more likely to receive sotorasib if they have the G12C mutation. If there are fewer patients with *KRAS* mutations in the docetaxel arm, this may serve to raise the ORR of the control arm, raising the bar for the experimental arm

Dr Herbst:
I think one has to be a little more scientific and ask why that patient is not responding [to immunotherapy]. Is it because they had issues with MHC or beta-microglobulin or something that was going to result in presentation issues? Is it a cold tumor? Half of lung tumors are cold with no TIL.

Emergence of Immunotherapy and Bispecifics in SCLC

EPICS

Regarding biomarkers in SCLC, the pathology expert mentioned that a major challenge is obtaining high-quality tissue; crush artifacts are common, which make even IHC difficult. However, genomic classification of SCLC is seen as a promising approach

The addition of immunotherapy to platinum-etoposide as first-line therapy in patients with extensive-stage SCLC is viewed by the experts as a modest advance; however, there is a small cohort that achieves a durable response

> Expert opinion is that tumors with the immunologically inflamed phenotype may have the most durable response to immunotherapy, and that a trial selecting for patients with these tumors may show a larger benefit with immunotherapy

The experts based on the West coast reported seeing more patients who have histologic transformation to SCLC from *EGFR* mutation-positive NSCLC than patients with de novo SCLC

> These patients are treated the same as de novo SCLC (ie, immunotherapy + chemotherapy); however, the experts discontinue osimertinib when giving immunotherapy

For patients with SCLC whose disease relapses after first-line therapy, the experts use a variety of approaches, including lurbinectedin, docetaxel, paclitaxel, gemcitabine, and topotecan

> There were differing experiences with lurbinectedin, with one of the experts having patients who do well, and another who reported that patients experienced fatigue, anorexia, and myelosuppression

DLL3 is still seen by the experts as a therapeutic target of interest in SCLC, despite the failure of Rova-T. Given that DLL3 is a target with good specificity for SCLC, there is support for testing different agents that can target DLL3 and deliver cytotoxic agents or immune cells

> ***Dr Hanna:***
> *. . . there is a small cohort in which [immunotherapy] is making a difference. Maybe it is the inflamed subset that Toni mentioned, and if you did a study only in that subset, maybe you'd see a big difference.*