EPICS

LUNG CANCER IN 2020 AND BEYOND

Chair: Corey J. Langer, MD, FACP

Confirmed faculty:

Nasser Hanna, MD – Indiana University, Simon Cancer Center
Roy Herbst, MD, PhD – Yale Cancer Center
Natasha Leighl, MD, FASCO – University of Toronto
Stephen Liu, MD – Georgetown University, Lombardi Comprehensive Cancer Center
Karen Reckamp, MD – Cedars-Sinai Medical Center
Naiyer Rizvi, MD – Columbia University, Herbert Irving Comprehensive Cancer Center
Mark Socinski, MD – AdventHealth Medical Group
Ignacio Wistuba, MD – MD Anderson Cancer Center
Antoinette Wozniak, MD, FACP, FASCO – UPMC Hillman Cancer Center

AGENDA

Day 1 – November 6, 2020; 1.00 PM – 5.00 PM

Time	Topic	Speaker/Moderator
1.00 PM – 1.05 PM (5 min)	Welcome and Introductions	Corey J. Langer, MD, FACP
1.05 PM – 1.15 PM (10 min)	**Prognostic and Predictive Biomarkers in NSCLC – Clinical vs Research Relevance (excluding *EGFR*/*ALK*)** • Review existing evidence for the following predictive and prognostic biomarkers in NSCLC (nonsquamous and squamous) – Histology (squamous vs nonsquamous) – Oncogenic drivers ▪ *KRAS* (G12C) ▪ *BRAF*-V600E ▪ *RET* ▪ *ROS1* ▪ *NTRK* ▪ *MET* amplification/skip mutations – Markers ▪ *HER2* ▪ *CEACAM5*	Ignacio Wistuba, MD

1.15 PM – 1.45 PM (30 min)	**Key Questions and Topics for Discussion** • What is the role of PET-CT for biomarker testing in lung cancer? • How well are we managing the trade-offs between tissue-availability and biomarker testing in academic and community practice today? What best and bad practices have emerged in this context? • What are the key differences in molecular testing between NSCLC and SCLC? Between nonsquamous and squamous? • How difficult is it to integrate another biomarker into NSCLC practice? • What proportion of patients do not have sufficient tissue (quantity and/or quality) available for all biomarker testing? Is there prioritization? What is your default diagnostic/therapeutic option in the absence of biomarker testing data? • How do liquid and tissue biopsies complement each other? • Given the increasing number of oncogenic drivers with approved targeted therapies, do single-gene tests still have a role, or should multigene panels become standard? • What are the main challenges or barriers to molecular testing in later lines of therapy? • Should *KRAS* G12C mutation testing now be standard? What about *NTRK* gene fusion testing or *HER2* mutation testing? • Are *MET* gene amplification, HER2 overexpression, and/or CEACAM5 actionable targets?	
1.45 PM – 1.55 PM (10 min)	**New Directions for *EGFR*-Mutant NSCLC** • Current TKIs (osimertinib, dacomitinib, erlotinib, afatinib, gefitinib), including OS data – Mention ADAURA data in addition to stage IV studies • Combinations with chemotherapy and/or antiangiogenic agents • *EGFR* exon 20 • Resistance mechanisms to EGFR TKIs • New antibodies (eg, HER3 ADC U3-1402) • Multikinase inhibitors	Natasha Leighl, MD, FASCO
1.55 PM – 2.30 PM (35 min)	**Key Questions and Topics for Discussion** • What is the preferred treatment sequencing for *EGFR*-mutated NSCLC? Does this differ according to the different mutation types? • Is there still a need to find a regimen better than osimertinib in stage III or metastatic disease?	

	• How to incorporate IO and TKI into patient care for those with driver mutations? Which patients should be given IO first? Which patents should be given TKI first? • What is the role of first-line combinations with antiangiogenic agents? • Is there any remaining role for first/second-generation TKIs? • What are your current testing practices with patients who progress on osimertinib (testing vs no testing; tissue vs liquid)? • In those that you are testing, what are you seeing in terms of mutations (*C797S* and other on-target mutations)? • What is your preferred approach after resistance to osimertinib – chemotherapy doublet; IMpower150, other? • What efficacy (ORR, PFS) would you like to see for a TKI that covers *C797S*, sensitizing mutations, and *T790M* in a patient population post osimertinib? • How do you view 4th-generation EGFR TKIs vs osimertinib combinations to address osimertinib-relapsed/refractory patients? • How do you manage CNS metastases at diagnosis? During EGFR TKI therapy? • What about concurrent upfront chemotherapy + TKI? • What is your approach for less-common *EGFR* mutations (eg, *L861Q*, *G719X*, *S768I*; exon 20 insertions) or *HER2* mutations? • Will immunotherapy ever have a role in patients with *EGFR* mutations?	
2.30 PM – 2.50 PM (20 min)	**Therapeutic Landscape for Rearranged NSCLC: The Emergence of RET and NTRK Inhibitors, and Are We "Full of" ALK Inhibitors?** *ALK* • Alectinib • Brigatinib • Lorlatinib • Ceritinib • Crizotinib • Ensartinib *NTRK* fusion • Entrectinib • Larotrectinib *RET* fusion • Selpercatinib • Pralsetinib	Antoinette Wozniak, MD, FACP, FASCO

	ROS1 rearrangement • Crizotinib • Entrectinib • Lorlatinib	
2.50 PM – 3.20 PM (30 min)	**Key Questions and Topics for Discussion** • How do you sequence the ALK inhibitors? Do the results of the CROWN trial influence your treatment decision making? • Is there any role for combinations (eg, chemotherapy, antiangiogenics with ALK inhibitors)? • What is your strategy for alectinib failure? • Is it feasible to clinically define the activity of ALK TKIs against various ALK resistance mutations to aid sequencing in subsequent lines of therapy? • Should rebiopsy be standard of care in *ALK*-rearranged NSCLC upon acquired resistance? Does liquid biopsy have a role? • What affects selection of entrectinib and larotrectinib in lung cancer with *NTRK* gene fusions? • Given there are multiple selective RET inhibitors now available, how do you determine the appropriate RET inhibitor for your patient(s)? • What additional data would you like to see with pralsetinib and/or selpercatinib? • How do you perceive differences in the RET inhibitors in terms of – CNS activity – QTc prolongation, hypersensitivity, pneumonitis? • Will you use a RET inhibitor in combination with other TKIs? • Will you use a RET inhibitor as first-line therapy in patients with a *RET* fusion? • Would you use 2 RET inhibitors in sequence?	
3.20 PM – 3.30 PM (10 min)	**BREAK**	
3.30 PM – 3.45 PM (15 min)	**Inhibiting Oncogenic Mutations: Overcoming Mutant KRAS, RTKs, and BRAF** *KRAS G12C and other mutations* • Sotorasib (AMG 510) – incl data from ESMO 2020 • MRTX849 – incl data from ENA 2020 Oct 2020 • BI 1701963 • JNJ-74699157 *HER2* mutations	Karen Reckamp, MD

	• DS-8201 • T-DM1 • TKIs *MET* exon 14 mutations • Capmatinib • Tepotinib • Crizotinib • Savolitinib *BRAF* mutations • Dabrafenib/trametinib • Vemurafenib	
3.45 PM – 4.15 PM (30 min)	**Key Questions and Topics for Discussion** • Which line of therapy is most promising for KRAS inhibitors? What are the endpoints that need to be met to change practice? • For 1L KRAS inhibitors, what is the appropriate control? • How would you compare the efficacy and safety of AMG 510 with MRTX849? – How do you view the ORR reporting (unconfirmed with MRTX and confirmed with AMG)? – Please comment on deaths from pneumonitis, GI, and liver toxicity • What are your efficacy expectations for emerging *KRAS* G12C inhibitors in second line, on the basis of recent data? • Is *KRAS* G12C single-agent activity "enough"? If not, what are the most promising partners for *KRAS* G12C inhibitors (IO? Chemo? SHP2? MAPK inhibitors, or other?) • Do you routinely test for *KRAS* G12C at diagnosis? How do you currently treat patients with this mutation? • What about *KRAS* mutations other than G12C? Do co-mutations affect response to KRAS inhibitors? • Which *HER2* mutations are important for ADCs? • How do we address ILD associated with anti-HER2 ADCs? • What is the status of *MET* amplification as a target? What is the best definition of "MET amplified"? Is tissue the only biopsy source to assess this? • What are the clinical strategies for *BRAF* non-V600E? • Is the role of immunotherapy changing/undergoing reconsideration in patients with certain oncogenic drivers?	

4.15 PM – 4.30 PM (15 min)	**Slicing the Squamous Pie: The "Other" Lung Cancer** • Immunotherapy – Single-agent: Pembrolizumab, atezolizumab, cemiplimab – IMpower131 – KEYNOTE-407 – CheckMate 227/9LA – For trials open to all histologies, please mention % squamous and how this may impact overall results – Other agents • Status of S1400 (MEDI4736, GDC-0032, palbociclib, and AZD4547) • Others?	Roy Herbst, MD, PhD
4.30 PM – 4.55 PM (25 min)	**Key Questions and Topics for Discussion** • What is your preferred first-line approach for squamous NSCLC that is locally advanced? That is metastatic? • In trials open to all histologies, how do you interpret the results based on the proportion of squamous NSCLC enrolled? • Are there any actionable markers in squamous NSCLC? Are single-gene tests possible in squamous NSCLC, or are multigene panels necessary? Does this remain purely investigational? • Given the mutational complexity of squamous NSCLC, how should we approach targeted therapy? • What is the current status of the Lung-MAP trial? What are its therapeutic implications? • Are there any promising combinations that would be interesting to study further for the treatment of squamous NSCLC? • How can we combine resources effectively to advance the field (eg, role of central banking and clinical trial access)? Is the Lung-MAP trial a paradigm for other trials in thoracic malignancies?	
4.55 PM – 5.00 PM (5 min)	Wrap-up and Overview of Day 2 Activities	Corey J. Langer, MD, FACP

AGENDA

Day 2 – November 7, 2020; 9.00 AM – 1.00 PM

Time	Topic	Speaker/Moderator
9.00 AM – 9.05 AM (5 min)	Review Agenda and Framework for Day 2	Corey J. Langer, MD, FACP
9.05 AM – 9.15 AM (10 min)	**Biomarkers for Immunotherapy: Making Sense of the Chaos** • PD-L1 • TMB (tissue vs blood based); efforts to harmonize TMB assays • *STK11* • *KEAP1* • Other correlates (T-cell exhaustion, gene expression, etc)	Roy Herbst, MD, PhD
9.15 AM – 9.40 AM (25 min)	**Key Questions and Topics for Discussion** • Is immunotherapy active in certain oncogenic drivers (*KRAS*, *BRAF*, *MET* exon 14)? • Given the emergence of targeted treatments for patients with specific biomarkers, what is the utility of PD-L1s in retreatment? • Does PD-L1 or TMB influence decision making in patients with an oncogenic driver? • Would your institution/pathology department use multiple PD-L1 assays if different regimens were tied to specific tests? • What picture is emerging from recent TMB analyses? Is blood-based TMB feasible? • Will PD-L1 be supplemented or supplanted by other potential biomarkers (eg, TMB, gene expression signatures)? • How will tissue/liquid/clinical (bio)markers be used for the selection of therapy? How do you see liquid biopsies being employed throughout the course of therapy (initial tx, PD, etc)? • Does TMB have any prognostic value in (N)SCLC, or any value in delineating study questions?	
9.40 AM – 9.55 AM (15 min)	**First-Line Immunotherapy: Single Agent or Combination?** • Single agents – KN24/KN42; CM26; IMpower110 (atezolizumab); EMPOWER-Lung 1 (cemiplimab) – M7824 (TGF-beta/PD-L1) • IO/chemotherapy – KN189 – IM150 – CM9LA • IO/IO	Mark Socinski, MD

	– CM227 • New approaches – TIGIT (eg, tiragolumab, vibostolimab) – IL-2 (NKTR-214) – IO/targeted therapy • Approaches in marker-negative patients	
9.55 AM – 10.40 AM (45 min)	**Key Questions and Topics for Discussion** • What is the role of cemiplimab in the treatment landscape relative to other agents? • Do any of the following differentiate cemiplimab from other anti–PD-(L)1 agents? – Efficacy/safety data – The rate of crossover in EMPOWER-Lung 1 • What is the importance of broader inclusion criteria that were part of the design of the EMPOWER-Lung 1 trial? • What drives treatment decision and choice between PD-1 monotherapy vs chemo combo in patients with PD-L1 TPS >1% or >50%? • How do you manage patients with PD-L1 ≥50% in whom molecular testing results are still pending, but who need treatment? • How well are patients with low/no PD-L1 being served by anti–PD-(L)1 drugs today? Does the platinum doublet remain a standard for clinical development in this population? • How do you manage immunotherapy-ineligible patients? Is this a shrinking population? • Do you routinely use TMB and or *STK11* in clinical decision-making? • Which chemotherapy backbones are the best partners for immunotherapy? • What is the ideal sequence of cytotoxic/checkpoint inhibitors? • Have you used 1L nivolumab/ipilimumab +/- chemotherapy? How do you select patients? • What do you think the potential of M7824 in 1L NSCLC? • What's your take on the recent news (10/21) that M7824/bintrafusp passed futility in 1L NSCLC, but trial was not expanded?	
10.40 AM – 10.50 AM (10 min)	**New Directions for Second-Line Therapy** • Chemotherapy after immunotherapy (eg, docetaxel, rechallenge with carboplatin) • Antiangiogenic agents • Targeting Trop2 (eg, DS-1062) • Immunotherapy combinations – ILT4 (MK-4830; ESMO 2020, #524O) • S1400 trial	Naiyer Rizvi, MD

10.50 AM – 11.10 AM (20 min)	**Key Directions and Topics for Discussion** • What are appropriate second-line treatments for patients receiving immunotherapy + chemotherapy combinations in first line? • Does time to progression (durability or primary resistance) impact second-line treatment options? • How should we manage PD-L1–negative patients in the second line and beyond? • How should we manage resistance to immune checkpoint inhibitors? • Should we test patients who progress for biomarkers? • Should biomarker selection be used in combination therapies, even though early data suggested activity regardless of PD-L1 expression levels? • What about immunotherapies in combination with antiangiogenics? • What is the potential for combining immune checkpoint inhibitors with vaccines or other immunotherapeutic strategies? • With the emergence of upfront immunotherapy, has docetaxel-ramucirumab moved from third-line to second-line SOC?	
11.10 AM – 11.20 AM (10 min)	**BREAK**	
11.20 AM – 11.30 AM (10 min)	**Emergence of Immunotherapy and Immunoconjugates in SCLC** • Immunotherapy (IMpower133; CASPIAN) • Pretreated patients (eg, nivolumab, pembrolizumab) • Lurbinectedin • New targets – *DLL3* – *MET/RON* – *EZH2* – *EphB4* – PARP	Stephen Liu, MD
11.30 AM – 11.55 AM (25 min)	**Key Questions and Topics for Discussion** • [If including meso: What are your perspectives on the approval of nivolumab/ipilimumab?] • Given the results of IMpower133 and CASPIAN, what is your standard first-line approach for extensive-stage SCLC? • What will be the standard approach for previously treated SCLC? • What are the challenges for tissue-based biomarker testing in SCLC?	

	• Would you consider using another immunotherapy treatment (nivo +/– ipi; pembro) after first-line immunotherapy-chemotherapy? • What is the place of lurbinectedin in SCLC? Would you use as a single agent or with doxorubicin? • What are your thoughts on novel agents targeting DLL3? • What are your thoughts on bispecific antibodies and CAR T cells in SCLC? Is CRS a drawback in this disease? • What are your thoughts on PARP inhibitors in SCLC? • What are your thoughts on patient selection for immunotherapy in SCLC? Is PD-L1 [or TMB] a relevant marker? • Are there clinical scenarios where you would not give immunotherapy in SCLC? • What is the best setting/combination strategy for new agents?	
11.55 AM – 12.00 PM (5 min)	**What is the New First-Line Standard of Care for Mesothelioma?** • CheckMate 743 • PrE0505 • Ongoing DREAM3R trial design	Antoinette Wozniak, MD, FACP, FASCO
12.00 PM – 12.15 PM (15 min)	**Key Questions and Topics for Discussion** • Is nivolumab-ipilimumab the new first-line SOC in mesothelioma? Does histology matter? • Is there a subset (eg, older patients, PD-L1 0%, pure epithelioid) not well served by ipi-nivo? • Should certain subsets of mesothelioma be treated as distinct disease entities?	
12.15 PM – 12.25 PM (10 min)	**Immunotherapy in the Curative Setting: Stage I–III NSCLC** • Unresectable stage III – PACIFIC • Resectable – CheckMate 816 – LCMC3 – NADIM – NEOSTAR	Nasser Hanna, MD
12.25 PM – 12.55 PM (30 min)	**Key Questions and Topics for Discussion** • What is your assessment of the OS benefit seen in PACIFIC? • Does it concern you that baseline PET imaging was not routinely performed in PACIFIC? • How does PD-L1 status factor in your decision to use immunotherapy in stage III NSCLC – would you offer durvalumab if PD-L1 ≤1%?	

	• Would you use consolidation durvalumab in a patient with *EGFR* mutations? • How do you choose therapy after progression on consolidation durvalumab in unresectable stage III NSCLC? • Is post-chemoradiotherapy the best timing for immunotherapy in stage III disease? What are your thoughts about this approach vs concurrent CRT-IO or a neoadjuvant approach? • What is the role of immunotherapy-based combinations in unresectable stage III NSCLC after CRT? • What endpoints should be used for trials of perioperative immunotherapy (eg, MPR, pCR)?	
12.55 PM – 1.00 PM (5 min)	Conclusions and Wrap-up	Corey J. Langer, MD, FACP

ONCOBOARD

1. What are the key parameters that guide your selection among immunotherapy options for the first-line treatment of NSCLC?
2. The uptake of immune checkpoint inhibitors in early treatment of lung cancer has created a growing population of immunotherapy-resistant/refractory disease. What therapies are most promising in this post-immunotherapy space? Are there any promising new agents coming to market in the next 5 years that could be adopted in this space?
3. How do the following parameters affect your interpretation of clinical trials: breakdown of trial populations, early stopping of a study because of efficacy or futility, crossover (and the motivation to cross over)?
4. What is the optimal endpoint in neoadjuvant trials? Is MPR ready for prime time?
5. What emerging unmet needs are there in lung cancer?

Other questions to be developed if additional topics emerge.