Lung Cancer Live Chat Summary

Lung Cancer: Early Stage – Dr. Gilberto Lopes

Key Takeaways:

- **Neoadjuvant/Perioperative Immunotherapy:** New data confirm the benefits of combining immunotherapy with chemotherapy in both neoadjuvant and adjuvant settings. Notably, this strategy has shown the first evidence of **improved overall survival (OS)** in early-stage NSCLC.
- **Adjuvant ICI vs. Neoadjuvant/Perioperative Approaches:** Dr. Ricciuti pointed out that adjuvant immune checkpoint inhibitors (ICIs) have not demonstrated an OS benefit, arguing that **neoadjuvant/perioperative strategies should be favored** for early-stage lung cancer.
- **ALINA Trial & ALK-Positive NSCLC:** Alectinib has been established as the standard adjuvant treatment for ALK-positive NSCLC in the US and other countries. However, the absence of chemotherapy in the Alectinib arm raises concerns about abandoning adjuvant chemotherapy altogether, given its OS benefit.
- **LAURA Trial & Osimertinib in Locally Advanced Disease:** The use of osimertinib as consolidation therapy after chemoradiation in locally advanced NSCLC demonstrated **an impressive PFS improvement (HR 0.16)**. Dr. Ricciuti emphasized the need for **mature OS data** and questioned whether these findings could be extrapolated to other rare driver mutations where randomized trials may not be feasible.

Final Thoughts:
Dr. Lopes' presentation underscored multiple **practice-changing trials** from the past year, shaping treatment strategies in early-stage NSCLC. The discussion highlighted the evolving role of **immunotherapy and targeted therapies**, while also raising critical questions about **optimal sequencing and patient selection**.

Advanced NSCLC – Dr. Charu Aggarwal

Key Takeaways

- **LAURA Trial: Osimertinib significantly improved progression-free survival (PFS) in unresectable stage III EGFR-mutated NSCLC post-chemoradiotherapy (39.1 months vs. 5.6 months; HR 0.16).**
- **CROWN Trial: Lorlatinib outperformed crizotinib in ALK-positive NSCLC, with 5-year PFS rates of 60% vs. 8%. It also showed superior intracranial efficacy, but long-term toxicity remains a concern.**

- **MARIPOSA-2 Trial: Amivantamab plus chemotherapy, with or without lazertinib, improved PFS (HR 0.48 and 0.44) and response rates in EGFR-mutant NSCLC after osimertinib progression.**

Discussion Highlights

- **Osimertinib in LAURA: Experts noted the strong PFS benefit, but emphasized the need for overall survival (OS) data to confirm long-term impact.**
- **Lorlatinib in CROWN: While highly effective, toxicity remains a limitation. Newer ALK inhibitors may offer similar efficacy with better tolerability.**
- **Amivantamab combinations: Show promise post-osimertinib, but toxicity profiles require careful management.**

Conclusion

The session highlighted significant advancements in targeted therapy for advanced NSCLC, particularly for EGFR- and ALK-mutant disease. While new treatments offer better disease control, long-term safety and optimal treatment sequencing remain key challenges.

Small Cell Lung Cancer and Mesothelioma – Dr. Jarushka Naidoo

Key Takeaways

- **SCLC Treatment Landscape:**
    - **Extensive-Stage (ES) SCLC:**
        - **First-line (1L):** Chemo-immunotherapy remains the **standard of care (SOC)** with **IMpower133 (Atezolizumab + EP)** and **CASPIAN (Durvalumab + EP)**.
        - **Second-line (2L):** Options include **lurbinectedin** and **tarlatamab**.
    - **Limited-Stage (LS) SCLC:**
        - **ADRIATIC trial: Durvalumab consolidation is now the new SOC.**
        - **LU005 trial: Concurrent immunotherapy with chemo-radiotherapy did not improve OS.**
    - **Future Directions:**
        - **DELPHI-305:** First-line **maintenance tarlatamab** in development.
        - **Other novel agents** (e.g., iDXD) are being explored.
- **Mesothelioma Overview:**
    - **Diagnosis remains challenging** due to its occupational exposure link.

- **Localized Disease:**
  - Surgery may no longer be the primary approach except for select patients.
  - **Role of radiotherapy (RT) is being reconsidered.**
- **Advanced Disease:**
  - **First-line: Ipilimumab + Nivolumab (Ipi/Nivo)** or **Pemetrexed + Chemotherapy** remain key options.
  - **Potential new therapies are emerging.**

Lung Cancer Radiotherapy – Dr. Henning Willers & Dr. Katie Keane

Key Takeaways

- **PACIFIC-2 & PACIFIC-4 Trials:**
  - **PACIFIC-2** showed negative results for **concurrent chemo-radiotherapy (chemoRT) with immunotherapy (IO)**, potentially due to differences in patient populations, increased toxicity, or changes in the **tumor microenvironment (TME)**.
  - **PACIFIC-4**, which evaluates IO in the **consolidative** setting after **SBRT (stereotactic body radiotherapy),** is still awaited. Previous **MERCK and SWOG trials** with concurrent IO were negative.
- **Radiotherapy Strategies in Locally Advanced NSCLC (LA-NSCLC):**
  - **Lymph node sparing radiotherapy** is being explored, as standard radiation may be **immunosuppressive**.
  - **Local treatment intensification** may be necessary, with **SBRT and PET-guided dose escalation (SIB) as promising options.**
  - **Osimertinib after chemoradiotherapy** significantly improved **progression-free survival (PFS)** in **stage III EGFR-mutated NSCLC** (LAURA trial).
  - **Micrometastatic disease remains a challenge**—local intensification alone is insufficient.
  - **Timing of intervention at maximal TKI response** (potentially guided by **PET or ctDNA**) is a key area of research.
- **SCLC Radiotherapy Considerations:**
  - **ADRIATIC trial:** Consolidation **durvalumab for 2 years post-chemoRT** is now **the standard of care (SOC)** in **limited-stage SCLC (LS-SCLC)** with significant **PFS and OS benefit.**

  - **High recurrence rates (3-6 months)** raise questions about subsequent treatment strategies.
  - **Prophylactic cranial irradiation (PCI) vs. MRI surveillance:**
    - **Role of PCI remains uncertain** as **immunotherapy benefits were observed in both PCI and non-PCI groups.**
    - Ongoing trials are comparing **PCI vs. MRI surveillance**.
    - **If PCI is omitted, MRI every 3 months** is recommended due to the **high risk of brain metastases.**

Conclusion

This session highlighted the **evolving role of radiotherapy in NSCLC and SCLC,** emphasizing the need for **better strategies to manage micrometastatic disease, optimize timing of interventions, and refine PCI approaches.** While **consolidation immunotherapy is now SOC for LS-SCLC, challenges remain in balancing toxicity, recurrence risk, and treatment sequencing.**

Lung Cancer Pathology & Diagnostics – Dr. Umberto Malapelle

Key Takeaways:

- **Challenges in Molecular Testing & False Negatives:**
  - A **critical issue in lung cancer diagnostics** is the risk of **false negatives for less common alterations**, such as **rare EGFR exon 20 insertions, uncommon fusions, or splicing site variants**.
  - Ensuring **the correct reference laboratory and methodology** is crucial to achieving an **accurate diagnosis**, which in turn leads to **appropriate therapy selection**.
- **Blood vs. Tissue Testing for EGFR Mutations:**
  - **EGFR testing** can be performed on both **tissue and blood (liquid biopsy)**.
  - **Plasma-based next-generation sequencing (NGS)** or **droplet digital PCR (ddPCR)** offers a **faster turnaround time** and is often used in parallel with tissue-based testing.
- **Tissue vs. Liquid Biopsy – When to Use Which?**
  - **Tissue biopsy is generally preferred** because it provides more detailed insights, particularly in cases of **acquired resistance to targeted therapies**.
  - Tissue biopsy is essential for detecting **histologic transformations** and alterations that liquid biopsy might miss, such as **gene amplifications (e.g., MET, HER2)**.

    - However, **plasma NGS can be useful in capturing genomic heterogeneity**, as it samples circulating tumor DNA rather than a single lesion.

Discussion Highlights:

- **Parallel Testing Strategy**: When possible, **running both tissue and liquid biopsy in parallel** can provide complementary insights, improving diagnostic accuracy.
- **Multidisciplinary Approach**: The **integration of pathology into oncology discussions** was highlighted as essential for accurate diagnosis and treatment planning.

Conclusion:

The session underscored the **importance of high-quality molecular testing** in lung cancer. While **tissue remains the gold standard**, **plasma NGS** offers advantages in terms of speed and capturing tumor heterogeneity. A **parallel testing approach**, when feasible, can improve diagnostic accuracy and ensure patients receive the most **effective, personalized treatment**.

Mucositis – Dr. Paolo Bossi & Dr. Hannah Wardill

Key Takeaways:

- **Understanding Mucositis & Its Impact:**
    - **Mucositis affects the entire gastrointestinal (GI) tract**, with different approaches required for treatment depending on the **site (oral vs. lower GI)** and the type of **cancer therapy (chemotherapy, radiotherapy, targeted therapies, immunotherapy)**.
    - It remains **one of the most challenging and debilitating toxicities** of cancer treatment, significantly impacting patients' quality of life.
- **Microbiome's Role in Mucositis Prevention:**
    - **Preclinical research has shown that microbiome diversity and composition** play a fundamental role in reducing oral mucositis caused by chemoradiation.
    - The **first randomized trial demonstrated that SSk12 (a probiotic strain) effectively reduces mucositis**, highlighting the **potential of microbiome modulation** in supportive care.
- **Risk Factors for Severe Mucositis:**
  Patients at **higher risk** include:
    - **Very young or elderly patients**
    - **Those with poor oral hygiene**
    - **Patients with concurrent infections (e.g., Candida overgrowth)**

    - **Patients on antibiotics prior to treatment**
    - **Patients using medications that cause xerostomia (dry mouth)**

- **The Role of Technology & Biology in Reducing Mucositis:**
    - **Proton therapy** could theoretically reduce oral mucositis by delivering more precise radiation therapy.
    - **Radiotherapy modulation based on hypoxia (using FMISO PET imaging)** could help **tailor treatment intensity** and **reduce toxicity**.

Discussion Highlights:

- **Multidisciplinary Approach in Mucositis Management**:
    - Effective mucositis prevention requires collaboration between **radiation oncologists, dentists, and oral hygienists**.
    - Some countries, such as Sweden, **subsidize dental care** for patients undergoing chemoradiation, ensuring **better preventive measures**.
- **Laser Therapy for Mucositis from Antibody-Drug Conjugates (ADCs):**
    - ADCs, such as **Dato-DxD**, have been associated with **Grade 2-3 mucositis**.
    - **Laser therapy is used in some countries**, but **substantial clinical data is still lacking** on its effectiveness in preventing ADC-induced mucositis.
- **Microbiome Modulation – Are We Ready?**
    - While **the importance of the microbiome is well recognized**, the **optimal formulation of probiotics and postbiotics** for mucositis prevention is **not yet approved** for routine use.
    - Research in this area is advancing, and implementation in clinical practice may not be far off.

Conclusion:

The session highlighted **mucositis as a major toxicity of cancer treatment** that requires **site-specific and therapy-specific management strategies**. Research is increasingly focusing on **microbiome modulation, advanced radiotherapy techniques, and novel supportive care approaches** to mitigate mucositis. While **technology and biology** hold promise, **further clinical validation** is needed to optimize prevention and treatment strategies.

ADC Toxicities – Dr. Maryam Lustberg

Key Takeaways:

- **Early recognition and intervention are critical** for managing **antibody-drug conjugate (ADC) toxicities**.
    - **Therapy interruption, steroid initiation, and close monitoring** are essential strategies to mitigate severe adverse effects.
    - Both **patients and healthcare teams need to be well-informed** about potential ADC-related complications.
- **Rechallenge Considerations:**
    - **Rechallenge may be considered for fully resolved Grade 1 toxicities.**
    - **There is currently no safe protocol** for rechallenging patients with **unresolved Grade 1 toxicities or any Grade 2 toxicities.**
    - **Combining ADCs with immunotherapy requires additional safety and management considerations**, as it can compound toxicity risks.
- **Wearable Devices for Early Detection:**
    - **There is growing interest in wearable technology** to help **detect ADC toxicities early**, particularly **interstitial lung disease (ILD)**.
    - However, these technologies are **not yet ready for routine clinical use**.

Discussion Highlights:

- **Sex Differences in ADC Toxicity:**
    - **Women appear to experience ADC-related adverse events (AEs) more frequently than men.**
    - Possible explanations include:
        - **Differences in body composition**, leading to **higher relative drug exposure** in women.
        - **Variations in drug metabolism and clearance**, as seen with other systemic therapies like fluorouracil.
        - **Potential biases in adverse event reporting**, where men and women may perceive and report symptoms differently.
        - **Differences in hematologic toxicity rates**, as objectively measured AEs were more common in women.
- **The Need for Better Risk Prediction & Preventive Strategies:**
    - **Identifying patients at higher risk** of ADC toxicities remains a key goal.
    - More research is needed to **develop tailored monitoring and preventive strategies** for high-risk patients.

Conclusion:

This session underscored the **importance of early toxicity management, risk assessment, and patient education** in ADC therapy. While **wearable technology and rechallenge protocols** are being explored, they are not yet standard practice. **Sex-based differences in ADC toxicities highlight the need for further research** to improve individualized patient care.