Liquid Biopsy in NSCLC
Molecular profiling & Research Use

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Dr. Pellini discloses:

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Outline

• ctDNA definition & sources of ctDNA
• ctDNA applications in oncology:
  o Molecular profiling
    ▪ Case 1 & 2 presentation
  o Treatment Monitoring
    ▪ 2023 ASCO updates
Tumor-derived fragments of nucleic acids identified in the blood are called circulating tumor DNA (ctDNA)

ctDNA Applications in Oncology

A) Molecular Profiling
- Tissue Based Approach
- TTF-1+, Napsin A+, Adenocarcinoma
- Liquid Biopsy Approach
- ctDNA

B) Treatment Response Monitoring
- ctDNA levels (VAF)
- EGFR L858R
- EGFR T790M

C) Detection of Minimal Residual Disease
- Diagnosis
- Curative Intent Multimodal Therapy
- Serial Monitoring of ctDNA
- MRD Detection
- Radiographic Progression

D) Early Cancer Detection

Shields M, Chen K…Pellini B. Int J Mol Sci. 2022
Stage IV NSCLC (Guardant 360) Liquid biopsy NGS assay that offers comprehensive testing for 74 genes most relevant to solid tumors.

Leighl N et al. Clin Cancer Res. 2019

ctDNA sequencing has high sensitivity and specificity to identify actionable genomic alterations
Case 1

- 08/03/2022: 79-year-old, never smoker male, left pleural effusion + consolidation on CT Chest.
- Bronchoscopy and Thoracentesis: Adenocarcinoma of Lung Primary. Negative Brain MRI.
- PD-L1 (IHC): Performed on pleural fluid = TPS 70 %.

08/26/2022: Liquid Biopsy (NGS testing) = No actionable mutations.

- (08/23/2022 – 10/02/2022): Patient was treated with single agent Pembrolizumab x 3 cycles.
- F/U CT TAP: Increased lung mass + pleural effusion = Disease progression.
- Patient referred to MCC for second opinion/clinical trial consideration.

09/20/2022: Pleural Fluid NGS testing. ERBB2/Her-2 Exon 20 insertion identified, GOF - oncogenic.
Case 1

• Patient was started on Fam-trastuzumab deruxtecan on 11/10/2022.

• 07/17/2023 - CT-TAP: Left lung scarring without measurable tumor. Improved left lower lobe aeration with decreased loculated effusion and no new metastases.
Case 2

- **06/29/2022**: 62-year-old woman presented with R hilar mass + R pleural effusion.
- Thoracentesis: Cytology = adenocarcinoma of lung.
- **07/25/2022**: CARIS testing on pleural fluid but limited tissue. PD-L1 = 1% TPS

- Treated with Carboplatin + Pemetrexed + Pembrolizumab and then maintenance Pembrolizumab + Pemetrexed

- **03/14/2023** - CT TAP: Worsening R pleural effusion. Concern for new hilar mets = Progressive disease

- MCC referral for 2nd line Tx with Amivantamab or Mobocertinib vs Clinical trial.
- Pre- Clinical trial work up = Repeat LN biopsy + (EGFR gene mutational analysis + solid tissue NGS)

- **Idylla EGFR Mutation Assay**: No EGFR mutations detected.
- **Comprehensive NGS testing on same core biopsy**: POSITIVE for EGFR exon 20 insertion.

- **04/06/2023** - Liquid Biopsy: NGS testing: EGFR exon 20 insertion identified.

- Patient enrolled in Clinical Trial MCC 20409 - 06/05/2023.
- **07/17/2023** - CT-TAP: Progressive disease
  - Discontinued from the trial and recommended to discuss next-line amivantamab vs. mobocertinib with her local oncologist.

- **04/06/2023** - Liquid Biopsy: NGS testing: EGFR exon 20 insertion identified.
ctDNA applications in oncology

A) Molecular Profiling
- Tissue Based Approach
- Liquid Biopsy Approach

B) Treatment Response Monitoring
- cDNA levels (VAF)
- Time (months)
- Diagnosis, Initiation of Targeted Therapy, Detection by Liquid Biopsy, Radiographic Recurrence
- EGFR L858R, EGFR T790M

C) Detection of Minimal Residual Disease
- Diagnosis, Curative Intent Multimodal Therapy, Serial Monitoring of ctDNA, MRD Detection, Radiographic Progression

D) Early Cancer Detection

Shields M, Chen K…Pellini B. *Int J Mol Sci.* 2022
ctDNA decrease ≥90% at week 3 or 9 during cemiplimab treatment is associated with improved OS

Advanced NSCLC
Tumor-informed assay (Signatera™ & FoundationOne Tracker)

Vokes N et al. 2023 ASCO Annual Meeting.
Circulating Tumor DNA Monitoring on Chemo-immunotherapy Informs Outcomes in Advanced Non-Small Cell Lung Cancer

Tumor-informed assay (FoundationOne Tracker)

Pellini B et al. Clin Cancer Res. 2023
Pellini B et al. *Clin Cancer Res*. 2023

**Tumor-informed assay**

*FoundationOne Tracker*

Additional cycles of induction therapy are not associated with improved outcomes in patients with ctDNA detection at C4D1.
Patients with undetectable **EGFR** 8 weeks after treatment start had better PFS and OS

Stage IV NSCLC
Tumor-naïve assay (Guardant 360)

Mack PC et al. *Clin Cancer Res.* 2022
Treatment escalation based on ctDNA detection is under investigation for patients with **EGFR** mutations

**NCT04410796**

**Screening:** Untreated metastatic EGFR+ NSCLC No prior treatment with EGFR TKI

- **Plasma EGFR testing**
  - **Negative:** (490 pts)
  - **Positive:**
    - **Cycle 1:** Osimertinib 80mg PO daily (571 pts)
    - **Cycle 2:**
    - **Cycle 3:**

- **Randomization 1:1**

- **EOT**
  - **Arm A:** Osimertinib 80mg PO daily (38 pts)
  - **Arm B:** Osimertinib 80mg PO daily + Carboplatin (AUC 5) and Pemetrexed (500mg/m2) x 4 cycles (38 pts)

- **Cycle 4-7**
  - **Arm A:** Osimertinib 80mg PO daily
  - **Arm B:** Osimertinib 80mg PO daily and Pemetrexed (500mg/m2) Maintenance therapy

**Drop-out:** (5 pts)

**Treatment plan:** All patients will receive osimertinib 80mg orally daily. Patients enrolled in Arm B will receive Carboplatin (AUC 5 IV q 3 weeks) and Pemetrexed (500mg/m2 IV q 3 weeks) for a total of 4 cycles followed by pemetrexed maintenance from cycle 8 onwards.

**Total enrollment:** Approximately 571 patients will be screened. 80 will be eligible for randomization and treatment consent. 76 will be randomized.

**Time to completion:** 5 years

National Study PI: Helena Yu, MD (MSKCC); Moffitt PI: Bruna Pellini, MD
Take home points

• Multiple technologies are available for plasma genotyping with variable sensitivity and specificity

• ctDNA can identify patients with advanced NSCLC who are responding to therapy (molecular response) at an early timepoint

• Ongoing trials will inform if clinical decision-making can be guided by ctDNA and if that improves patients’ outcomes
Questions?

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