IASLC WEBINARS
Updates on Liquid Biopsy for Advanced NSCLC:
A Consensus Statement From the IASLC

Presenters: Drs. Christian Rolfo, David R. Gandara and Natasha B. Leighl
Disclosures

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Consultant: EMD Serono, Pfizer, Mirati, Eisai, Daiichi Sankyo, Sanofi Genzyme-Regeneron
Speakers Bureau: Astra Zeneca, Roche, COR2ED

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Advisory Board: Roche Genentech, Merck, Novartis, Boehringer Ingelheim, Regeneron, Sanofi, Amgen
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Consultant: Adagene, Astra Zeneca, IO Biotech, Guardant Health, Oncocyte

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Honoraria for CME: BMS, MSD, Novartis, Takeda, Sanofi Genzyme
Consultant: CADTH, EMD Serono, GlaxoSmithKline, Puma Biotechnology

Murry Wynes, PhD - Nothing to Disclose

All other planners, reviewers and staff reported no relevant financial relationships.
All relevant financial relationships have been mitigated.
The Role of Liquid Biopsy at the time of Advanced NSCLC Diagnosis and Therapeutic Decision-Making

Natasha Leighl MD MMSc FRCPC FASCO
Princess Margaret Cancer Centre
Toronto, Canada
Case #1

- 58 year old woman from Angola, bank employee, ex-smoker (10 pack years, quit 10 years ago), presents with cough, ECOG PS 1, 10 lb weight loss over 9 months

- Family history of lung cancer (mother, age 59)

- Imaging reveals lung, liver and bone metastases.

- Review of Lung FNA (outside institution): adenocarcinoma, TTF-1+, CK7+, PD-L1 TPS 60%, tissue-based genomic testing ordered from FNA
Question 1: How would you proceed?

› 1. Start systemic therapy now with immunotherapy alone (pembrolizumab, atezolizumab or cemiplimab)?

› 2. Start systemic therapy now with immunotherapy plus platinum-based chemotherapy

› 3. Start systemic therapy now with platinum-based chemotherapy alone

› 4. Await tissue-based molecular results before starting therapy

› 5. Initiate liquid biopsy testing and await results before starting systemic therapy

› 6. Option 3 plus initiate liquid biopsy (without waiting on results)
When do you use liquid biopsy in your practice?

1. No routine use in clinic outside trials or research
2. To diagnose mechanisms of acquired resistance to targeted therapy
3. Genotyping of advanced NSCLC if tissue molecular testing insufficient
4. Genotyping of advanced NSCLC if tissue testing pending
5. Other
Diagnostic algorithm for liquid biopsy use in treatment-naive advanced/metastatic NSCLC

Advanced NSCLC with unknown genotype

Tissue sample available for tumor genotyping

Tumor tissue adequate for genotyping

Tumor tissue genotyping

cfDNA analysis in case of incomplete tumor genotyping

Tumor tissue scant/of uncertain adequacy for genotyping

Concurrent tumor tissue and cfDNA genotyping

“Sequential approach”

“Complementary approach”

Tissue sample unavailable for tumor genotyping

“Plasma first approach”

Plasma cfDNA genotyping

Re-biopsy for tumor tissue genotyping in case of absence of targetable drivers in plasma

Potential Barriers to Molecular Testing

Cost most frequently identified barrier to testing across all regions
- 63% report patient pays for testing

- Quality barriers include insufficient tissue, lack of assay sensitivity, inadequate technical expertise
- 58% indicated testing is not centralized in their country
- ~1/3 of respondents who request tests were unaware of the most recent guidelines
- 29% indicated turnaround time (ordering test to receiving report) of ≥10 days

Based on International Association for the Study of Lung Cancer survey including 2537 respondents from 102 countries.
VALUE: Demonstrating the VALUE of cfDNA testing in the Canadian public system for advanced NSCLC patients

**COHORT 1**
- Treatment naïve Stage IV non-squamous NSCLC patients
- ≤10 pack year smoking history
- N=150

**COHORT 2**
- NSCLC patients after TKI failure (excluding T790M screening)
- N=60

Blood-based ctDNA molecular profiling using the GUARDANT360™ assay

Tumour tissue profiling performed in all patients per institutional standard of care

PI: Leighl, Princess Margaret Cancer Centre; NCT03576937

**Clinical outcomes:**
- Best response
- Progression-free survival
- Time-to-treatment failure

**Patient, System outcomes:**
- Time-to-treatment start
- Incremental number of actionable alterations
- Quality of life (EQ5D), willingness-to-pay
- Cost-consequence analysis
ACTIONABLE TARGETS IDENTIFIED (N=146)

<table>
<thead>
<tr>
<th></th>
<th>SOC Tissue Testing</th>
<th>G360 Liquid Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>53</td>
<td>53</td>
</tr>
<tr>
<td>ALK</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>Insufficient DNA</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Not actionable</td>
<td>61</td>
<td>43</td>
</tr>
</tbody>
</table>

- **EGFR/ALK** were detected in 40% by TT and in 39% by G360.
- Other actionable alterations* were detected in 12% by TT, 18% by G360.
- No actionable alterations were detected in 42% by TT and 29% by G360.
- TT profiling unsuccessful in 6% of patients -- insufficient tissue/failed biopsy.
- 13% had no alterations detected by G360 (low disease burden or non-shedding tumour).

* Other actionable alterations **ROS1, EGFR** exon 20 insertion, **MET** exon 14 skipping mutation, **KRAS** G12C, and **ERBB2** exon 20 insertion.

Hao D... Leighl NB WCLC 2021
TISSUE AND LIQUID RESULTS HIGHLY CONCORDANT

Mismatch

- TT detected EGFR/ALK & G360 detected other actionable alteration
- 1%

- G360 detected & TT did not detect EGFR/ALK/other actionable alteration
- 16%

Concordant

- TT & G360 both detected EGFR/ALK
- 32%

- TT & G360 both detected other actionable alteration
- 9%

- TT detected & G360 did not detect EGFR/ALK/other actionable alteration
- 10%

* Other actionable alterations are ROS1, EGFR exon 20 insertion, MET exon 14 skipping mutation, KRAS G12C, and ERBB2 exon 20 insertion.

Liquid Biopsy “rescued” 16% of patients

TT alone (16)
- EGFR (16)
- ALK (1)
- ROS1 (3)
- EGFR ex20 ins (0)
- MET ex14 skip (2)
- KRAS G12C (0)
- ERBB2 ex20 in (0)

TT and G360 (60)
- EGFR (43)
- ALK (4)
- ROS1 (2)
- EGFR ex20 ins (5)
- MET ex14 skip (2)
- KRAS G12C (3)
- ERBB2 ex20 in (1)

G360 (24)
- EGFR (10)
- ALK (0)
- ROS1 (0)
- EGFR ex20 ins (2)
- MET ex14 skip (7)
- KRAS G12C (0)
- ERBB2 ex20 in (5)

TT: tumour testing; ins: insertion mutation; ex: exon; skip: skipping mutation
**Mean turnaround time:**

- **7.4 days** (SD+/-1.4) for G360
- **20.5 days** (SD+/- 9.9) for tissue profiling

**Treatment decisions were informed by:**

- G360 alone (38%)
- G360 plus TT results (31%)
- TT alone (26%)
- Neither (5%)

ICI: Immune checkpoint inhibitor; Chemo: Chemotherapy

Hao D… Leighl NB WCLC 2021
Response Rate, PFS, OS (N=122)

- ORR - Tissue Testing
- ORR - G360 Liquid Biopsy

Hao D... Leighl NB WCLC 2021; Updated Dec 2021
VALUE Economic Analysis

- Decision analytic Markov model compared:
  1. **Tissue biopsy alone versus**
  2. **Liquid biopsy in addition to tissue biopsy**

- Perspective: Canadian public health care system.
- Time horizon: lifetime (10 years).
- Genomic alterations were considered:
  - **Actionable** if approved or off-label targeted treatment available → **Targeted therapy**
  - **Non-actionable** if no targeted treatment available → **Chemo-immunotherapy**
## Results

<table>
<thead>
<tr>
<th>Stage IV NSCLC</th>
<th>Targeted therapy (n=82)</th>
<th>Non-targeted therapy (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95%CI)</td>
<td>11.4 (8.3 - not reached)</td>
<td>9.8 (4.4 – 19.5)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>Not reached</td>
<td>19.5 (10.2 – 19.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Testing strategy</th>
<th>Cost (CAD$)</th>
<th>QALY</th>
<th>Incremental cost (CAD$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid biopsy + Tumour tissue biopsy</td>
<td>1,305,524</td>
<td>7.17</td>
<td>Reference</td>
</tr>
<tr>
<td>Tumour tissue biopsy alone</td>
<td>1,342,740</td>
<td>7.10</td>
<td>37,216</td>
</tr>
</tbody>
</table>
What happened to our patient?

› Enrolled in VALUE study

› Day 5, pathologist reported insufficient tissue for genomic testing, repeat biopsy booked

› Liquid biopsy result in 7 days and began treatment on day 8
Began osimertinib treatment as part of a targeted therapy trial

Began in 2019, treatment ongoing
Case #1: Take Away Messages

- Plasma ctDNA is a new and valid tool for genotyping in patients with advanced NSCLC including –
  - Plasma-first approach to complement to tumor tissue profiling in treatment naïve patients, especially those with insufficient tissue, under-genotyped samples or insufficient time for tissue profiling
  - Adding liquid biopsy may yield cost savings (or at least cost neutrality) by avoiding inappropriate immunotherapy in patients with oncogene addicted lung cancer
IASLC Liquid Biopsy Webinar: Case 2 in Advanced NSCLC

Christian Rolfo, MD, PhD, MBA, Dr.hc.
Professor and Assoc. Director for Clinical Research
Center for Thoracic Oncology
The Tisch Cancer Institute
Icahn School of Medicine at Mount Sinai
Mount Sinai Health System
New York, NY, USA
Case presentation

- 52-year-old never smoker female
- July 2018: onset of left flank pain, dyspnea and cough → pleural effusion
- **Pleural fluid cytology:** positive for lung adenocarcinoma.
- **PET/CT imaging:** left upper lobe lung mass, left-sided pulmonary nodules, left-sided pleural effusion and lymphadenopathy along the left hilar, mediastinal, left mammary chain, porta hepatis and retroperitoneal regions.
- **MRI brain imaging:** 8mm right frontoparietal brain metastasis.
- **Tissue NGS (Foundation One):** *EGFR E746_A750del* (exon 19 deletion) mutation.
- **Guardant360 liquid biopsy** collected in July 2018: *EGFR* exon 19 deletion with 41.2% cell-free DNA (cfDNA).
Use of liquid biopsy in advanced NSCLC: When?

› 1- I only use it at Baseline to establish the presence of oncogene drivers

› 2- Only at Progression to determine mechanisms of resistance

› 3- After 6 weeks of treatment as monitoring

› 4- I use liquid biopsy in all these situations (1, 2, 3)

› 4- Never
In this case of advanced NSCLC harboring EGFR Exon19del and a small asymptomatic brain metastasis, what would be your choice of therapy?

1- SBRT to the brain metastasis and start osimertinib
2- Osimertinib alone
3- EGFR TKI + Bevacizumab
4- EGFR TKI + Platinum doublet Chemotherapy
She began osimertinib in August 2018, with an intracranial complete response and extracranial partial response noted.
EGFR-mutated NSCLC: FLAURA sub-analysis

a) Clearance of plasma EGFRm at week 3
b) Clearance of plasma EGFRm at week 6

Zhou C, et al. ASCO 2019
After 18 months of osimertinib therapy, restaging CT imaging in February 2020 revealed new subcentimeter left hilar lymph nodes.

Repeat liquid biopsy collected at that time revealed emergence of an $\text{EGFR C797S}$ mutation (0.3% cfDNA).

Bronchoscopy/EBUS were performed; station 11L lymph nodes were positive for metastatic adenocarcinoma.
Tissue vs. Liquid Biopsy

Tissue biopsy:
- FFPE samples
- Cytoblocks
- Pathology and IHC (PD-L1, ALK, ROS1)
- Tumor genotyping (NGS, RT-PCR, and/or FISH)

Advantages:
- Pathology information
- Assessment of DNA and non-DNA biomarkers
- PD-L1 assessment
- Longer TAT
- Limited tissue quantities
- Invasive
- AT PD, re-biopsy not always feasible
- Tumor heterogeneity

Disadvantages:
- Non-DNA biomarkers not evaluable
- Increased costs if used concurrently with tissue testing
- False negatives

Liquid biopsy:
- Plasma
- cfDNA
- Tumor genotyping (NGS, RT-PCR, digital PCR)

Advantages:
- High concordance rate
- Rapid TAT
- Minimally invasive
- Repeatable over time
- Better capture tumor heterogeneity and clonal evolution

Rolfo et al (Gandara), JTO Oct 2021
Treatment at Progression

In June 2020 CT scan showed the left hilar lymph node had increased in size. MRI showed no residual brain metastasis. The patient was clinically well. What is your choice for treatment at this time:

1- Continue with Osimertinib
2- Local treatment with radiotherapy and continue Osimertinib
3- Switch to chemotherapy
4- Start chemotherapy and immunotherapy
Case 2 continued

The patient received radiation therapy to the left hilar lymph node, completed in June 2020. Osimertinib was continued.
Liquid biopsy in July 2020 showed persistence of \textit{EGFR C797S} (5.2% cfDNA) and \textit{EGFR} exon 19 deletion (4.7% cfDNA) mutations.
Clonal evolution through EGFR Targeted therapy

Passaro A. et al (Rolfo C) ESMO Open 2020
Liquid Biopsy in Acquired Resistance to Targeted Therapy

Clonal evolution

Acquired mutations and/or copy number variation of the target gene

Activation of alternative pathways ("by pass track")

Stage IV NSCLC with oncogene-addicted tumor

CT scan re-staging: Progressive disease

Blood draw

cfDNA analysis

Tissue re-biopsy

FFPE sample

Histology transformation

Main liquid biopsy techniques used

NGS-based approaches:
- High sensitivity
- Multiplex
- Gene rearrangements
- Gene amplifications

PCR-based approaches:
- Variable sensitivity
- Single gene testing
- Only for mutations

Main techniques used for tumor tissue

NGS-based approaches:
- High sensitivity
- Multiplex
- Gene rearrangements
- Gene amplifications

FISH:
- Gene rearrangements & amplifications

PCR-based approaches:
- Variable sensitivity
- Single/Multiplex gene testing
- Only for mutations

IHC:
- Protein expression

Rolfo et al (Gandara), JTO Oct 2021
Acquired mechanisms of resistance to 1st line Osimertinib: The FLAURA analysis (LB)

- No evidence of acquired EGFR T790M
- The most common resistance mechanisms were MET amplification and EGFR C797S mutation
- Other mechanisms included HER2 amplification, PIK3CA and RAS mutations

Ramalingam SS, et al. ESMO 2018

Passaro A., Janne P, Mok T and Peters S. Nature Cancer 2021
PET/CT in August 2020: development of supraclavicular and mediastinal lymphadenopathy plus new bone lesions. Liquid biopsy in August 2020: increasing \textit{EGFR} exon 19 deletion mutation (58.3% cfDNA) and \textit{EGFR} C797S mutation (55.6% cfDNA).

<table>
<thead>
<tr>
<th>Genetic Alteration</th>
<th>% cfDNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{EGFR E746_A750del}</td>
<td>41.2%</td>
</tr>
<tr>
<td>\textit{EGFR C797S}</td>
<td>0.3%</td>
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<tr>
<td>\textit{EGFR C797S}</td>
<td>5.2%</td>
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<tr>
<td>ARID1A Q656E</td>
<td>ND</td>
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<tr>
<td>\textit{EGFR T790M}</td>
<td>0.4%</td>
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<tr>
<td>TP53 C275Y</td>
<td>ND</td>
</tr>
<tr>
<td>ARID1A F1728F</td>
<td>ND</td>
</tr>
<tr>
<td>TP53 S127F</td>
<td>6.5%</td>
</tr>
<tr>
<td>BRAF Amplification</td>
<td>ND</td>
</tr>
<tr>
<td>CDK6 Amplification</td>
<td>ND</td>
</tr>
<tr>
<td>\textit{EGFR Amplification}</td>
<td>ND</td>
</tr>
<tr>
<td>NTRK2 L699L</td>
<td>ND</td>
</tr>
<tr>
<td>\textit{EGFR N338N}</td>
<td>ND</td>
</tr>
<tr>
<td>FGFR1 V795I</td>
<td>ND</td>
</tr>
</tbody>
</table>
Treatment at Progression

Due to the impressive response with Osimertinib and the small amount of disease at progression, with brain control. What is your choice for treatment at this time:

1. Local treatment with radiotherapy to all sites and continue osimertinib
2. Switch to chemotherapy
3. Start chemotherapy and immunotherapy
4. Switch to another EGFR TKI
Case 2 continued

As the *EGFR C797S* mutation was felt to be the likely mechanism of resistance, osimertinib was discontinued and erlotinib was initiated in late August 2020.
EGFR resistance mutations in response to TKI treatment and sensitivity to subsequent therapies.

Niederst et al, CCR 2015
On liquid biopsy collected in October 2020, EGFR C797S and EGFR exon 19 deletion mutations were not detected. PET/CT in November 2020 showed complete resolution of previously noted intrathoracic lymphadenopathy and no new lesions.
Follow-up liquid biopsy in January 2021 showed recurrence of EGFR C797S (10.7% cfDNA) and EGFR exon 19 deletion (13.4% cfDNA), as well as emergence of EGFR T790M (9.6% cfDNA). Follow-up CT chest imaging in February 2021 showed new subcentimeter pulmonary nodules.
Erlotinib was discontinued and she was initiated on chemotherapy with carbo/pemetrexed.

<table>
<thead>
<tr>
<th>Genetic Alteration</th>
<th>% cfDNA or amplification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGFR E746_A750del</strong></td>
<td>41.2% 0.2% 4.7% 58.3% ND 13.4% ND 1%</td>
</tr>
<tr>
<td><strong>EGFR C797S</strong></td>
<td>ND 0.3% 5.2% 55.6% ND 10.7% ND 0.7%</td>
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<tr>
<td><strong>ARID1A Q456Q</strong></td>
<td>ND ND ND 0.2% ND 0.2% 0.3% 0.6%</td>
</tr>
<tr>
<td><strong>EGFR T790M</strong></td>
<td>ND ND ND ND ND 9.6% ND 0.4%</td>
</tr>
<tr>
<td><strong>TPS3 C275Y</strong></td>
<td>ND ND ND ND ND ND 0.1% 0.2%</td>
</tr>
<tr>
<td><strong>ARID1A F1728F</strong></td>
<td>ND ND ND ND ND ND 0.3% 0.2%</td>
</tr>
<tr>
<td><strong>TPS3 S127F</strong></td>
<td>6.5% ND 0.4% 7.6% ND 2.6% ND 0.2%</td>
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<td><strong>BRAF Amplification</strong></td>
<td>2.2% ND ND ND ND ND ND</td>
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<td><strong>NTRK2 L699L</strong></td>
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<tr>
<td><strong>EGFR N338N</strong></td>
<td>ND ND ND ND 0.1% ND ND</td>
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<tr>
<td><strong>FGFR1 V795I</strong></td>
<td>ND ND ND ND ND 0.1% ND</td>
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</table>
Immunotherapy in patients with EGFR mutation

Mazieres et al, Annals of Oncology 30: 1321–1328, 2019
Case #2: Take Home messages

- cfDNA is emerging as a good tool for the entire patient journey, including monitoring

- A validated comprehensive platform should be employed

- Report every anecdotal case!

- Do broad molecular testing on your patients! At least to know the ones will not response to Immunotherapy
IASLC Liquid Biopsy Webinar: Case #3 in Advanced NSCLC

David R. Gandara, MD
University of California Davis
Comprehensive Cancer Center
Case 3

- 64-year-old male with prior 15 pack-year smoking history, presents with cough & SOB
- CT scan: Imaging with LUL primary, mediastinal & hilar adenopathy, plus bilateral lung & bone metastases.
- Fine Needle Biopsy: NSCLC-adenocarcinoma (TTF1+)
- Brain MRI: no metastatic disease
64 y/o male with new diagnosis of stage IV lung adenocarcinoma with bilateral lung and bone metastases. PS=1.
You decide to perform broad comprehensive genomic profiling (CGP) for actionable molecular alterations. There is inadequate tissue for next-generation sequencing (NGS).

Question 1: How would you proceed with testing, given anticipated turn-around-times (TRT)?

1. Send plasma only for GCP by ctDNA NGS (~7-day TRT)
2. Repeat biopsy & send tumor tissue only for CGP by NGS (~20-day TRT)
3. Send both plasma ctDNA + repeat tissue biopsy for CGP by NGS (~20-day total TRT)
Case 3

- Molecular testing by plasma NGS comprehensive genomic profiling reveals: KRAS G12C mutation + STK11 mutations. These findings are duplicated in subsequent tissue NGS analysis.
- PD-L1 (22C3) TPS = 1%.
Updated IASLC Consensus Statement on Liquid Biopsy in NSCLC: 2021

Diagnostic algorithm for liquid biopsy use in treatment-naive advanced/metastatic NSCLC

Rolfo, Gandara et al. JTO 2021
Case 3

For this 63 y/o patient with stage IV lung adenocarcinoma, former smoker. PS=1. Testing: KRAS G12C/STK11-mutated & PD-L1 TPS = 1%

Question 2: What do you recommend for first-line therapy?

1. Sotorasib (AMG 510)
2. Pemetrexed/carboplatin/pembrolizumab (KN 189)
3. Nivolumab + ipilimumab (CM 227)
4. Paclitaxel/carboplatin/bevacizumab/atezolizumab (IMP 150)
5. Platinum chemotherapy X 2 cycles + nivolumab/ipilimumab (CM 9LA)
# Immunotherapy Therapeutic Landscape in Advanced NSCLC: 1st-Line Phase III Trials

## Clinical Trial Results of 1st line Checkpoint Immunotherapy in Advanced NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug (vs Chemo)</th>
<th>PD-L1 Selection</th>
<th>Line of Tx</th>
<th>Control</th>
<th>Primary Endpoint</th>
<th>HR-Primary Endpoint</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>KN024</td>
<td>Pembro</td>
<td>≥50%</td>
<td>1st</td>
<td>Plat Chemo</td>
<td>PFS</td>
<td>0.50</td>
<td>Positive</td>
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<tr>
<td>CM026</td>
<td>Nivo</td>
<td>≥5%</td>
<td>1st</td>
<td>Plat Chemo</td>
<td>PFS</td>
<td>1.15</td>
<td>Negative</td>
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<tr>
<td>MYSTIC</td>
<td>Durva or Durva-Tremi</td>
<td>≥25%</td>
<td>1st</td>
<td>Plat Chemo</td>
<td>PFS &amp; OS</td>
<td>NR</td>
<td>Negative</td>
</tr>
<tr>
<td>KN189 (Non-SQ)</td>
<td>Pembro-Chemo</td>
<td>≥1%</td>
<td>1st</td>
<td>Plat Chemo</td>
<td>PFS</td>
<td>0.52</td>
<td>Positive</td>
</tr>
<tr>
<td>KN042</td>
<td>Pembro</td>
<td>≥1%</td>
<td>1st</td>
<td>Plat Chemo</td>
<td>OS</td>
<td>0.81 for OS 0.69 for 50%</td>
<td>Positive</td>
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<tr>
<td>KN047 (SQ)</td>
<td>Pembro-Chemo</td>
<td>None</td>
<td>1st</td>
<td>Plat-Nab Paclitaxel</td>
<td>PFS &amp; OS</td>
<td>0.64 for OS</td>
<td>Positive</td>
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<tr>
<td>Impower 150 (Non-SQ)</td>
<td>Atezo +Bev/Pac/Carbo</td>
<td>None</td>
<td>1st</td>
<td>Bev/Pac Carbo</td>
<td>PFS OS</td>
<td>0.71</td>
<td>Positive</td>
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<tr>
<td>Impower 131 (SQ)</td>
<td>Atezo + Nab/Carbo</td>
<td>None</td>
<td>1st</td>
<td>Pac/Carbo</td>
<td>PFS,OS</td>
<td>0.71 (PFS)</td>
<td>Positive</td>
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<tr>
<td>CM227</td>
<td>Nivo or Nivo-Ipi</td>
<td>&lt;1%/1% &amp; TMB≥10</td>
<td>1st</td>
<td>Plat Chemo</td>
<td>PFS &amp; OS</td>
<td>0.58 (in H-TMB)</td>
<td>Positive</td>
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<tr>
<td>IMPower 110</td>
<td>Atezo</td>
<td>≥1%</td>
<td>1st</td>
<td>Plat Chemo</td>
<td>OS in TC3/IC3</td>
<td>0.59</td>
<td>Positive</td>
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<tr>
<td>CM-9LA</td>
<td>Nivo-Ipi-Chemo</td>
<td>None</td>
<td>1st</td>
<td>Plat Chemo</td>
<td>OS</td>
<td>0.66</td>
<td>Positive</td>
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<tr>
<td>EMPOWER-lung1</td>
<td>Cemiplimab</td>
<td>≥50%</td>
<td>1st</td>
<td>Plat Chemo</td>
<td>OS,PFS</td>
<td>0.57</td>
<td>Positive</td>
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</tbody>
</table>

Adapted from Gandara: ELCC 2021

### Parameters

**Test Regimen**
- CPI Monotherapy
- CPI+Chemo
- CPI+Chemo+Bev
- CPI + CTLA4

**Biomarker**
- None
- PD-L1
- TMB

**Histology**
- All
- Squamous
- Non-Squamous

**Primary Endpoint**
- PFS
- OS
- Both
Stage IV NSCLC: Biomarker-driven Therapeutic Landscape Algorithm

Treatment-naïve NSCLC

Non-squamous

EGFR, ALK, NTRK, BRAF, or ROS1 +
Targeted Therapy

PD-L1 >50%

PD-L1 1-49%

PD-L1 <1%

TMB low

TMB high

TMB low

TMB high

I-O Monotherapy
PD-L1 ≥50%

I-O + Chemo
PD-L1 1-49% & PD-L1 <1%

I-O + I-O
TMB high Or PD-L1 ≥1% Or PD-L1 <1%

I-O + Chemo
PD-L1 1-49% & PD-L1 <1%

I-O + I-O
TMB high Or PD-L1 ≥1% Or PD-L1 <1%

Non-squamous

PD-L1 >50%
Pembro +/- Chemo
Atezo +/- Chemo

PD-L1 1-49%
Pem-Carbo-Pembo (KN-189)
Pac-Carbo-Bev-Atezo (IMpower150)

PD-L1 <1%

PD-L1 ≥50%
Pembro +/- Chemo
Atezo +/- Chemo

PD-L1 1-49%

PD-L1 <1%

PD-L1 ≥50%

PD-L1 1-49%

PD-L1 <1%

I-O + Chemo
PD-L1 1-49% & PD-L1 <1%

I-O + I-O
TMB high Or PD-L1 ≥1% Or PD-L1 <1%

I-O + Chemo
PD-L1 1-49% & PD-L1 <1%

I-O + I-O
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I-O + Chemo
PD-L1 1-49% & PD-L1 <1%

I-O + I-O
TMB high Or PD-L1 ≥1% Or PD-L1 <1%

EGFR, ALK, NTRK, BRAF, or ROS1 +
Targeted Therapy

NGS; TMB/PD-L1

Gandara ELCC 2021. (Adapted from S Peters: ILCC 2020)
CodeBreak100: Phase 2 Trial of Sotorasib in KRASP.G12C NSCLC

Sotorasib was orally administered at 960 mg once daily until disease progression\(^b\)

Radiographic scan every 6 weeks up to week 48 and once every 12 weeks thereafter

**Primary endpoint:** ORR (RECIST 1.1) by blinded independent central review

**Key secondary endpoints:** DoR; disease control rate; TTR; PFS; OS; safety

**Exploratory endpoints:** Evaluation of biomarkers (PD-L1, co-occurring mutations)

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Li BT et al. WCLC 2020. Abstract PS02.07
CodeBreak100: Depth of Tumor Response

Tumor shrinkage of any magnitude was observed in 81% of patients (101/124)
Median percentage of best tumor shrinkage among all responders was 60%

ORR: 37% (46/124)
Case 3

The patient is treated with pemetrexed/carboplatin/pembrolizumab & achieves a partial response.

However, at 6 months there is progressive disease in 3 sites (2 new bone lesions & growth of a pulmonary nodule from 1 to 2.5 cm.
In this case with KRAS G12C/STK11-mutated & PD-L1 TPS = 1%:

Question 3: Which do you recommend for at this point?

1. SBRT to all sites of PD & continue pemetrexed & pembrolizumab maintenance therapy.
2. Switch to sotorasib (AMG510).
3. Switch to docetaxel/ramucirumab.
4. Switch to nivolumab/ipilimumab.
Current Stage IV NSCLC Treatment Paradigm:
1\textsuperscript{st} \rightarrow 2\textsuperscript{nd} \rightarrow 3\textsuperscript{rd} Line Therapy

Stage IV NSCLC

- Mutation-negative PD-L1 \geq 50% → PD1/PD-L1 +/- Platinum-based Chemo
- Mutation-negative PD-L1 <50% → PD1/PD-L1 +/- Platinum-based Chemo • +/-CTLA4
- Actionable mutation → Targeted TKI

1L

1L

- Chemo (Docetaxel) +/- VEGFi (Ramucirumab)
- Targeted TKI (if available) • Chemo +/- VEGF • PD1/PD-L1

2L

3L+

- Chemo or other treatment dependent on prior therapy
• Patient sample size too small to draw firm conclusions, but
• **PD-L1 status:** ORR lowest in cases with PD-L1 50%
• **Co-Mutations:** ORR lowest in cases with KEAP1 mutation
Preliminary Exploratory Correlative Analysis of Co-Mutations with KRASG12C and Response Rate in Patients with NSCLC treated with Adagrasib

- High ORR (64%) in patients with tumors harboring STK11 and KRASG12C mutations
- No apparent trend with KEAP1, TP53, or other common mutations and response rate

Data as of 30 August 2020. Based on unaudited data.

Presented at the 32nd EORTC-NCI-AACR Symposium. October 24-25, 2020
Case #3: Take Home Messages

- Broad NGS Molecular Testing is now standard of care for advanced NSCLC patients at the time of initial diagnosis
- Treatment should not be initiated until Molecular Testing results are received
  - unless immediate treatment is considered an emergency
  - If emergency treated is started, it should be chemotherapy alone, not immunotherapy-chemotherapy, due to subsequent negative impact if targeted therapy required
- Not all oncogene drivers found on NGS testing are currently appropriate for 1st line therapy (e.g., KRAS G12C)
- While the presence of STK11 is a poor prognostic (and perhaps predictive) biomarker for checkpoint immunotherapy, early data suggest that co-mutation of STK11 with KRAS G12C does not adversely affect efficacy of G12C inhibitors