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

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INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

Disclosures

Christian Rolfo, MD, PhD, MBA, Dr.hc.

Consultant: EMD Serono, Pfizer, Mirati, Eisai, Daiichi Sankyo, Sanofi Genzyme-Regeneron

Speakers Bureau: Astra Zeneca, Roche, COR2ED

David R. Gandara, MD

Advisory Board: Roche Genentech, Merck, Novartis, Boehringer Ingelheim, Regeneron, Sanofi, Amgen

Research Grant: Amgen, Astex, Genentech

Consultant: Adagene, Astra Zeneca, IO Biotech, Guardant Health, Oncocyte

Natasha B. Leighl, MD, MMSc, FRCPC, FASCO

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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

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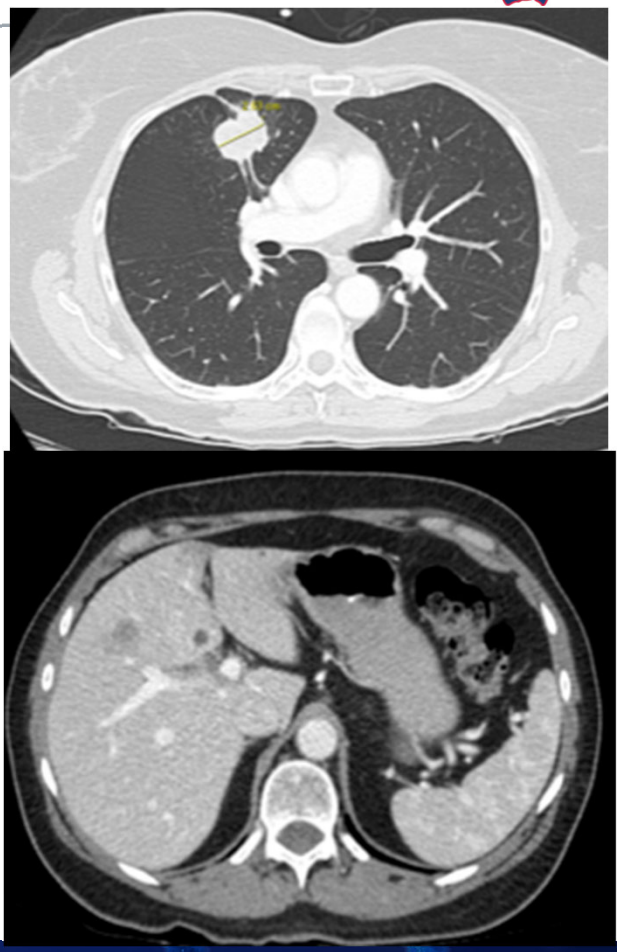
Case #1

- 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



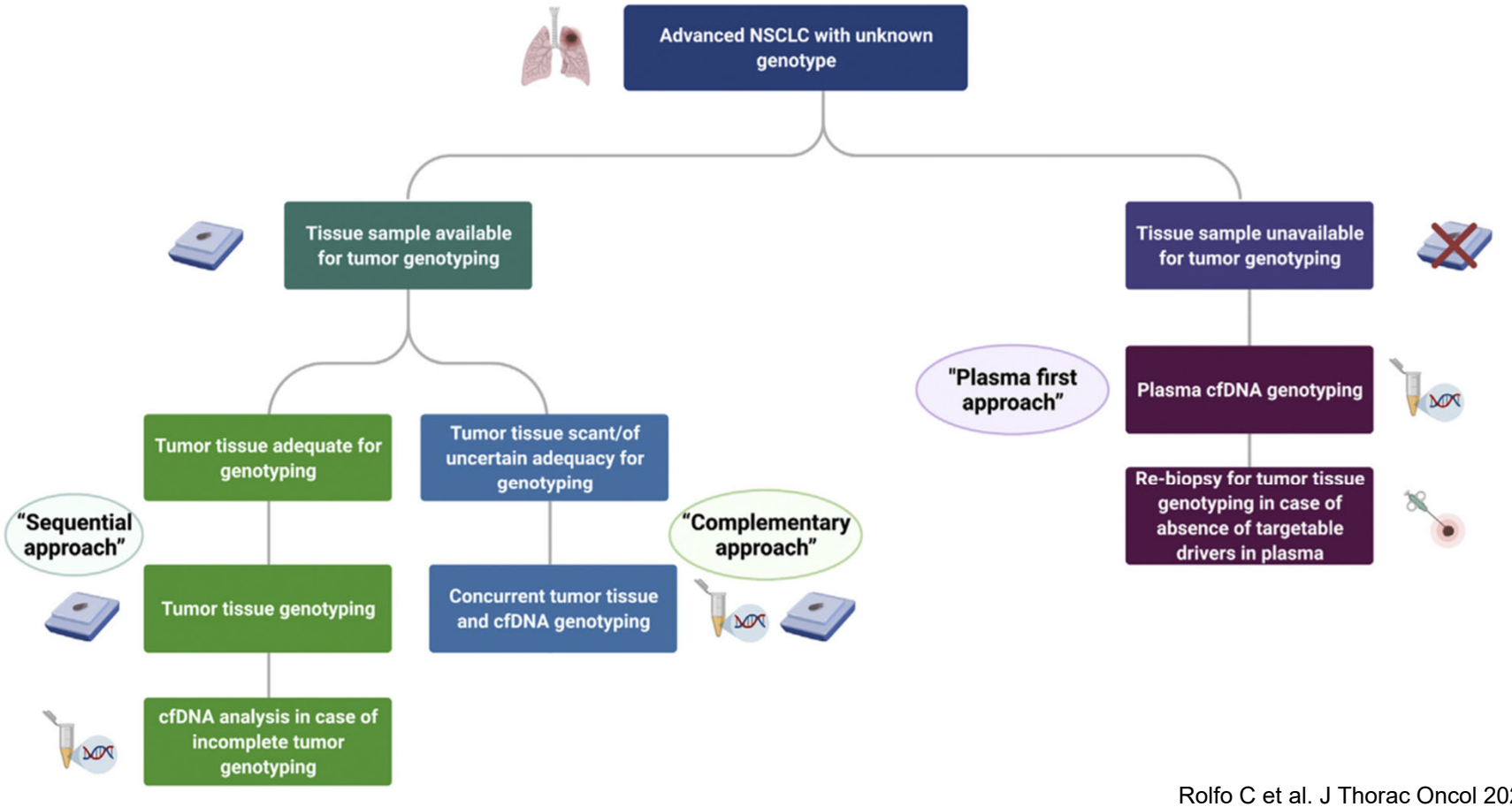
Question 1: How would you proceed?

- 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?

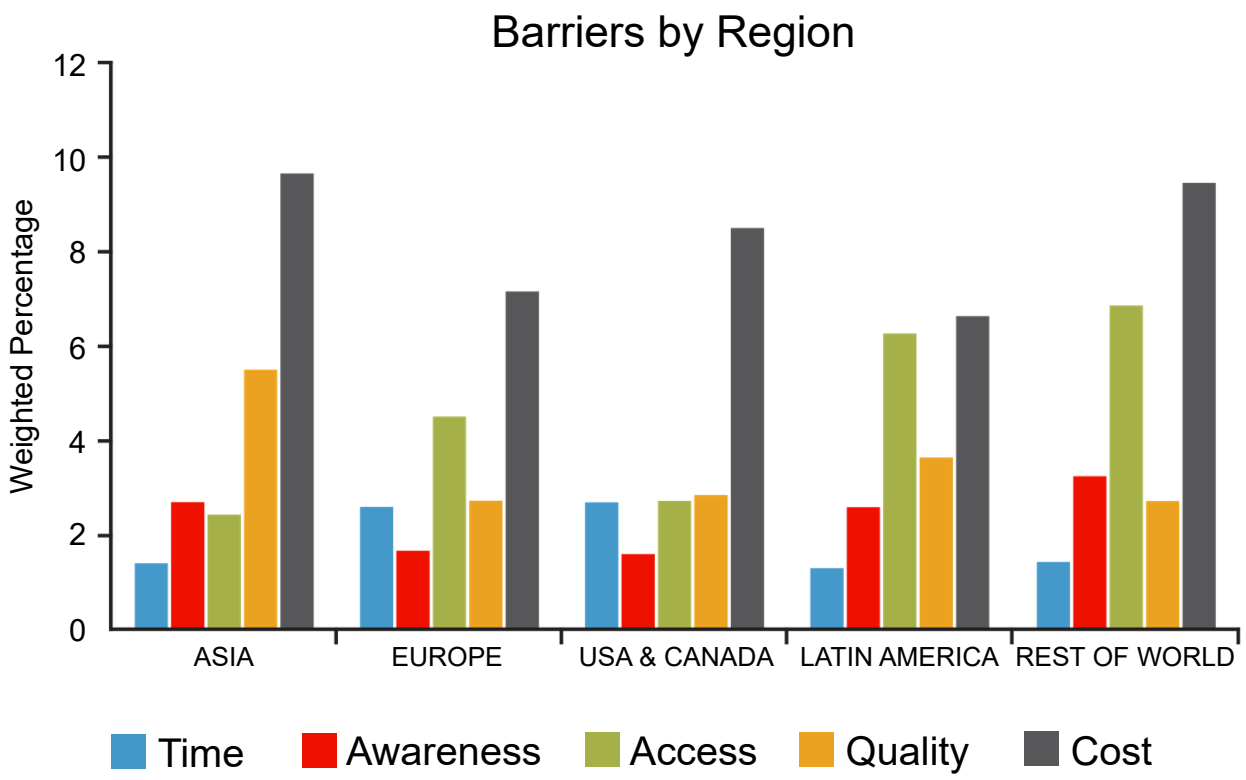
1. No routine use in clinic outside trials or research
2. To diagnose mechanisms of acquired resistance to targeted therapy
3. Genotyping of advanced NSCLC if tissue molecular testing insufficient
4. Genotyping of advanced NSCLC if tissue testing pending
5. Other

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



Rolfo C et al. J Thorac Oncol 2021; 16(10):1647–1662

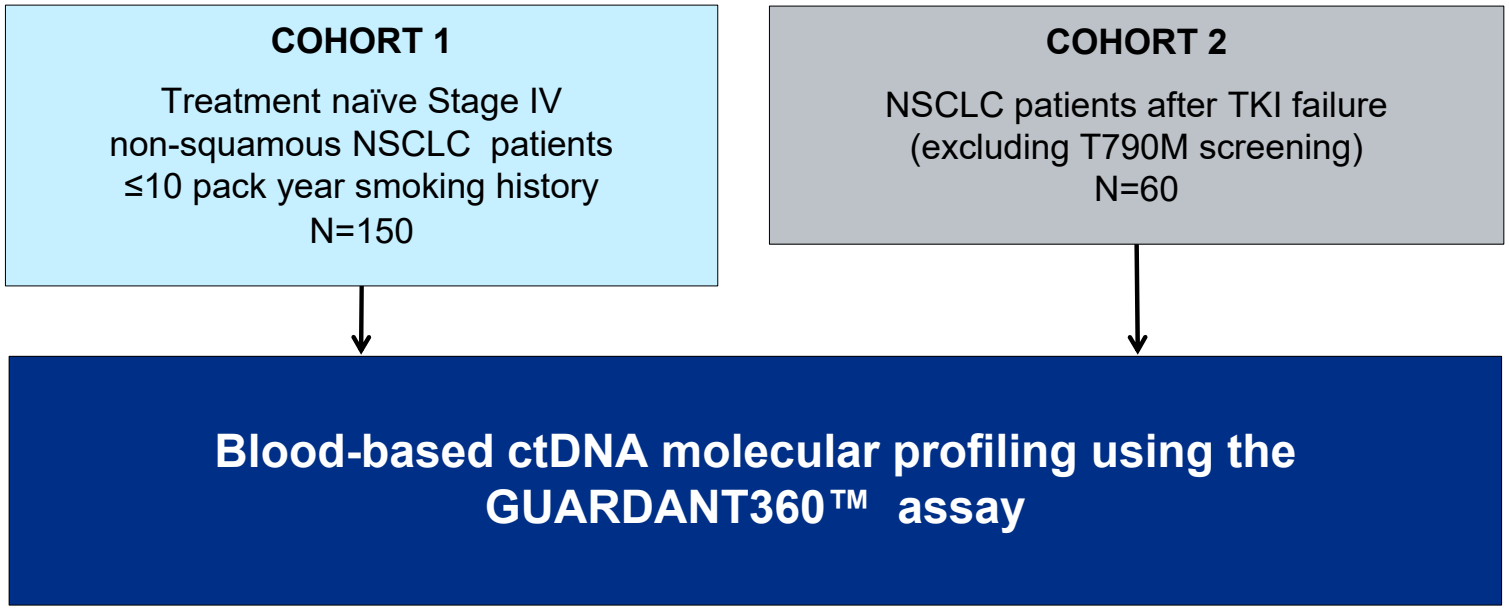
Potential Barriers to Molecular Testing



Based on International Association for the Study of Lung Cancer survey including 2537 respondents from 102 countries.
Smeltzer MP, et al. *J Thorac Oncol*. 2020;15:1434-1448.

- 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

VALUE: Demonstrating the VALUE of cfDNA testing in the Canadian public system for advanced NSCLC patients



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

PI: Leighl, Princess Margaret Cancer Centre; NCT03576937

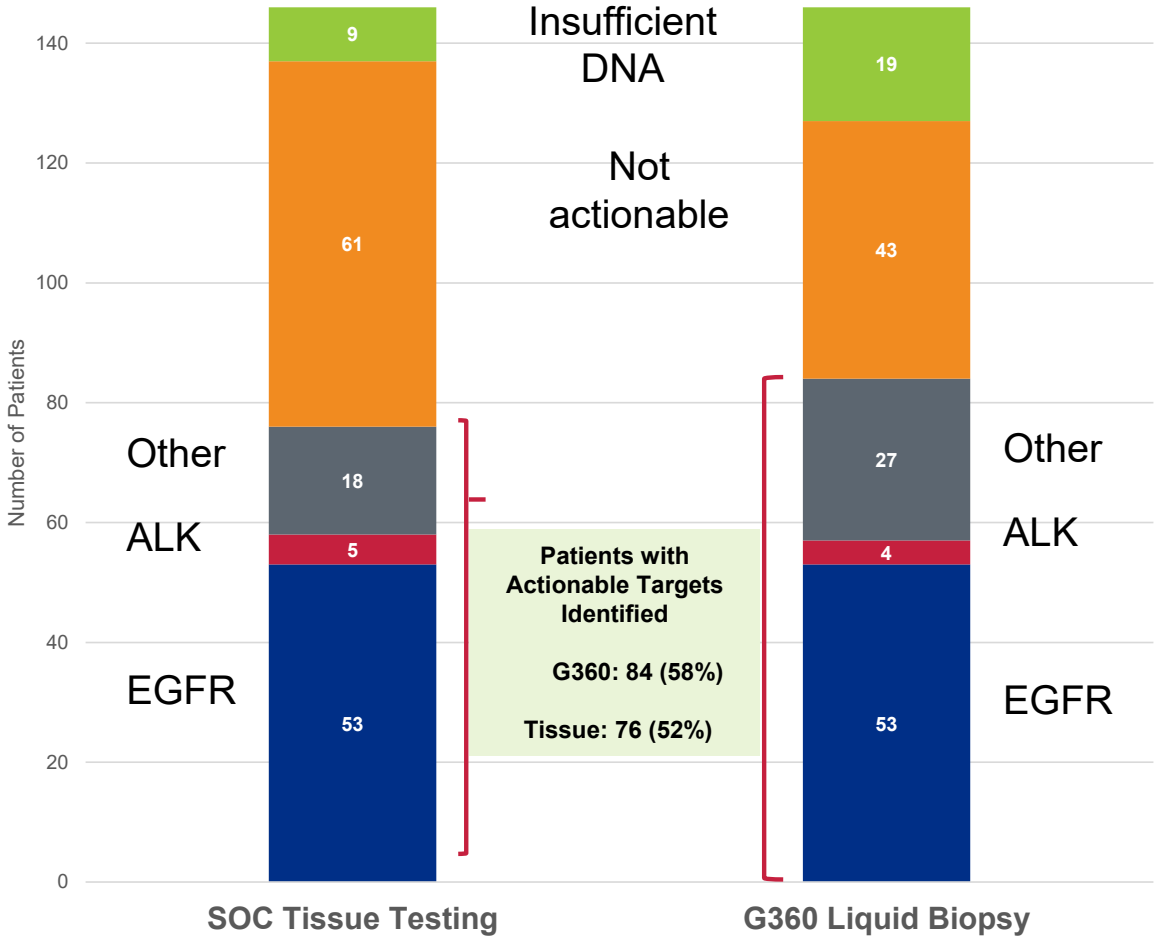
Clinical outcomes:

- 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)



- ***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.

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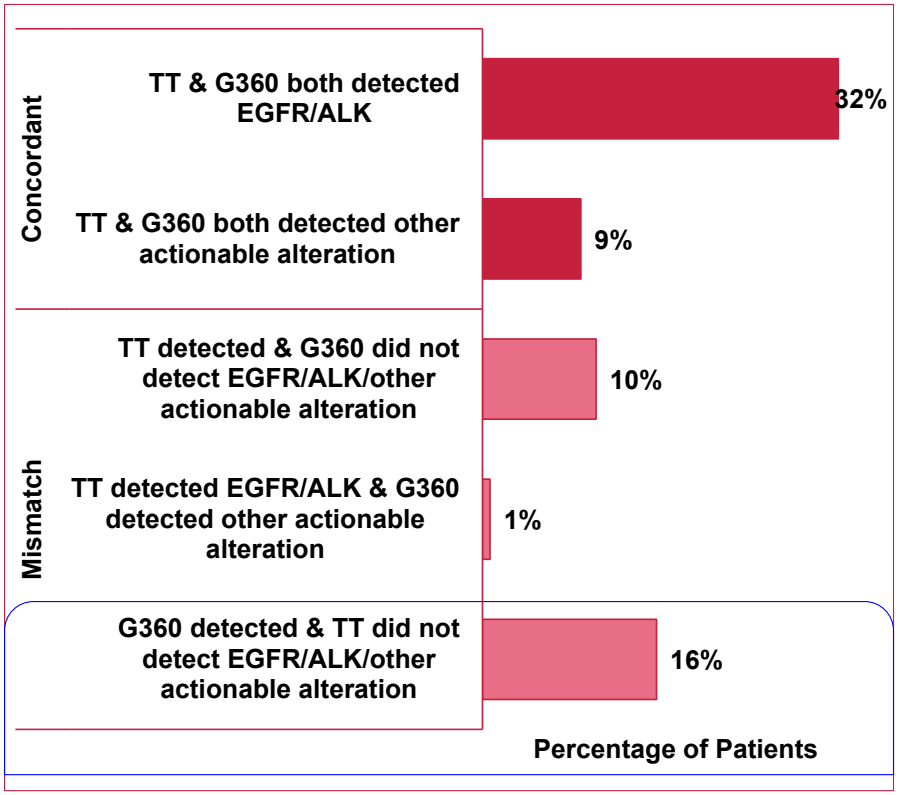
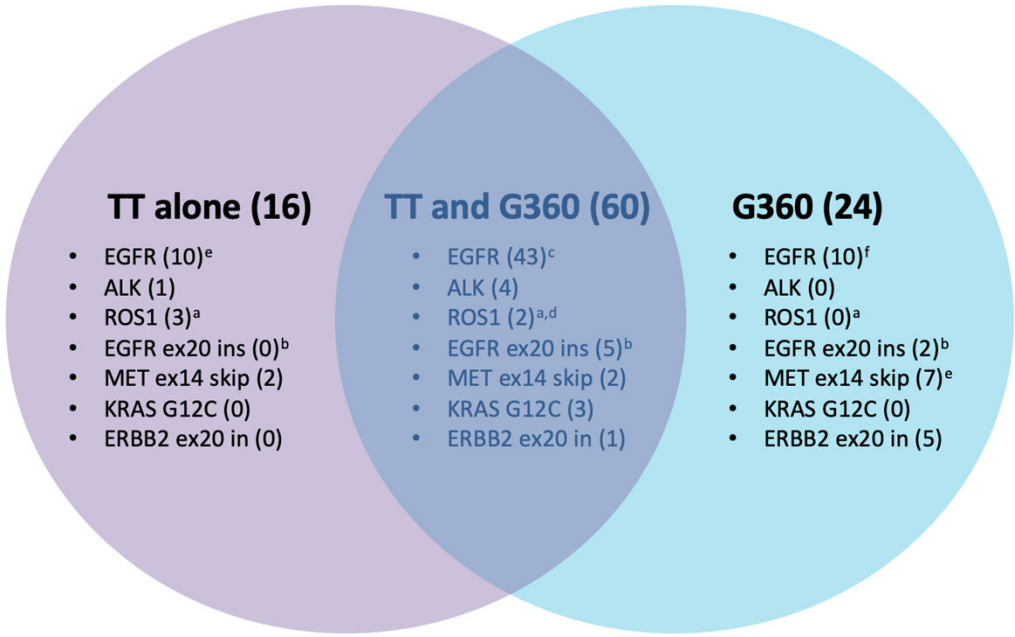
TISSUE AND LIQUID RESULTS HIGHLY CONCORDANT

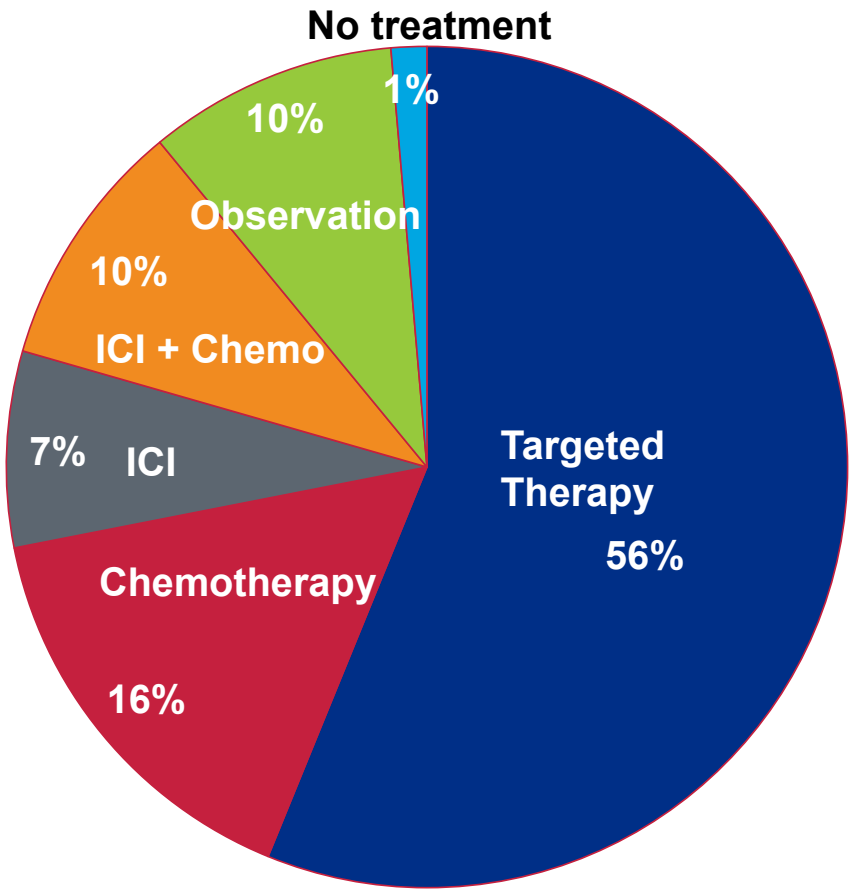


* Other actionable alterations are *ROS1, EGFR* exon 20 insertion, *MET* exon 14 skipping mutation, *KRAS* G12C, and *ERBB2* exon 20 insertion.

Liquid Biopsy "rescued" 16% of patients



TT: 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

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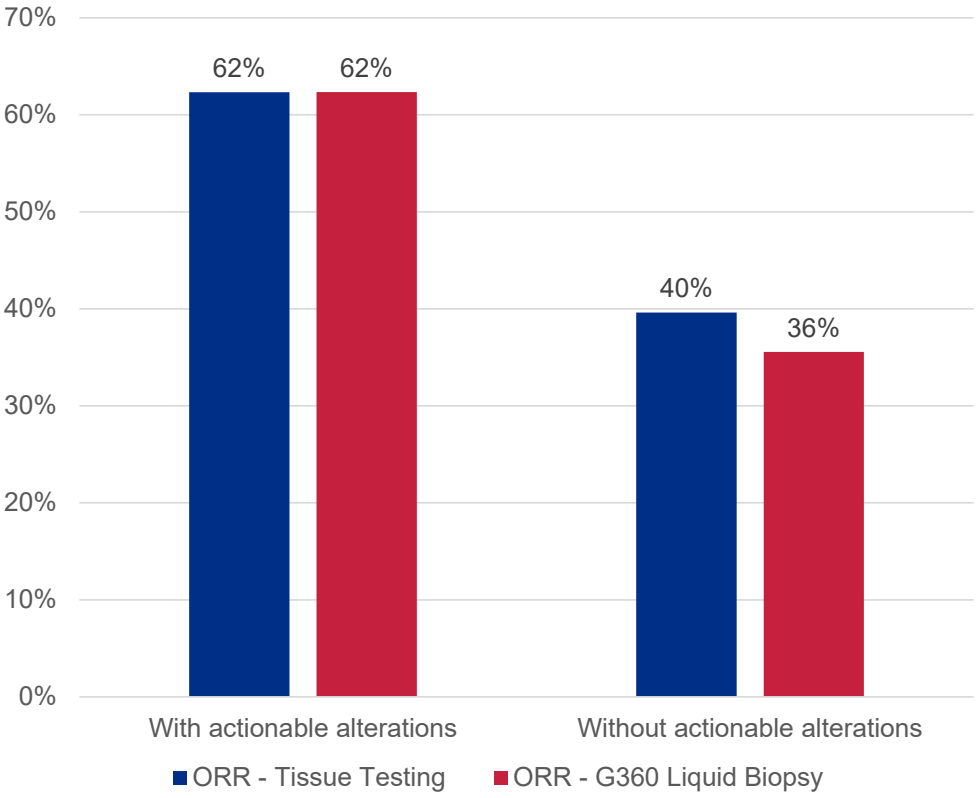
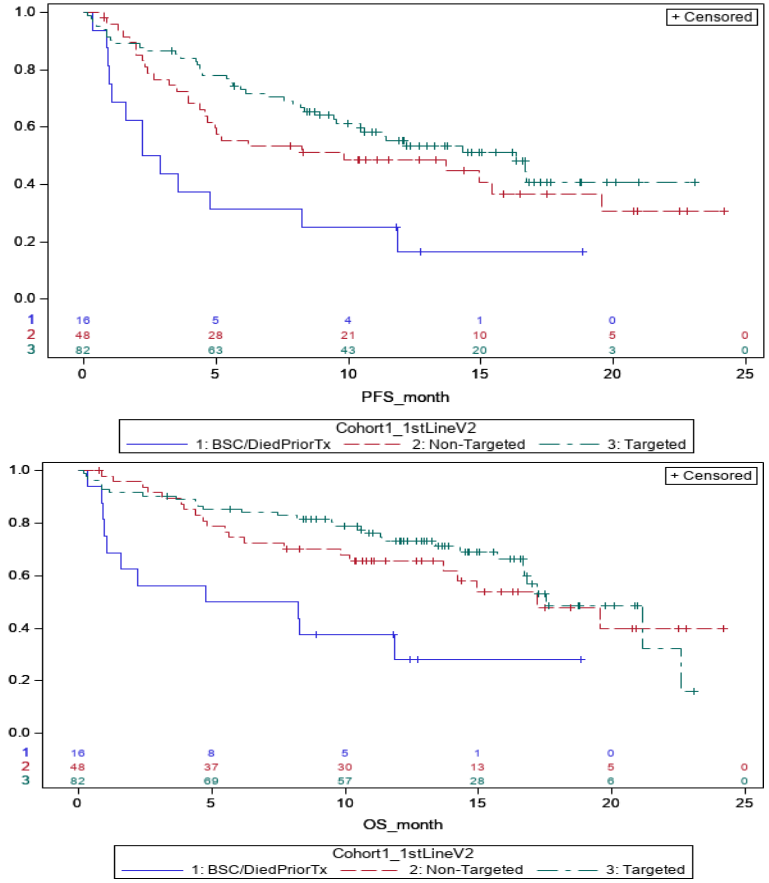
Response Rate, PFS, OS (N=122)

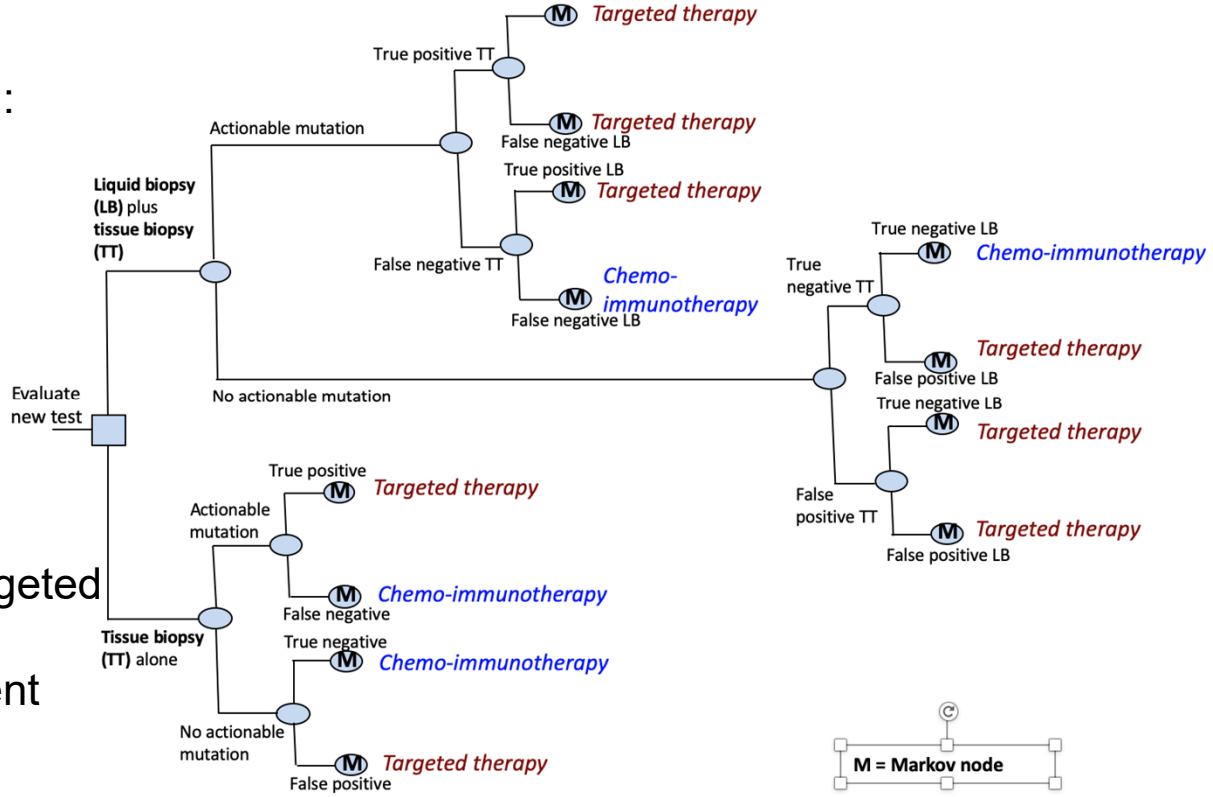




Hao D… Leighl NB WCLC 2021; Updated Dec 2021

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



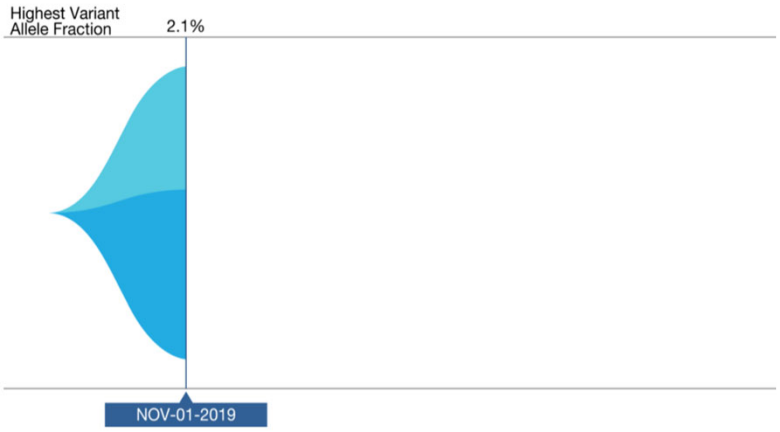
Results

Stage IV NSCLC	Targeted therapy (n=82)	Non-targeted therapy (n=48)
Median PFS, months (95%CI)	11.4 (8.3 - not reached)	9.8 (4.4 – 19.5)
Median OS, months (95% CI)	Not reached	19.5 (10.2 – 19.5)

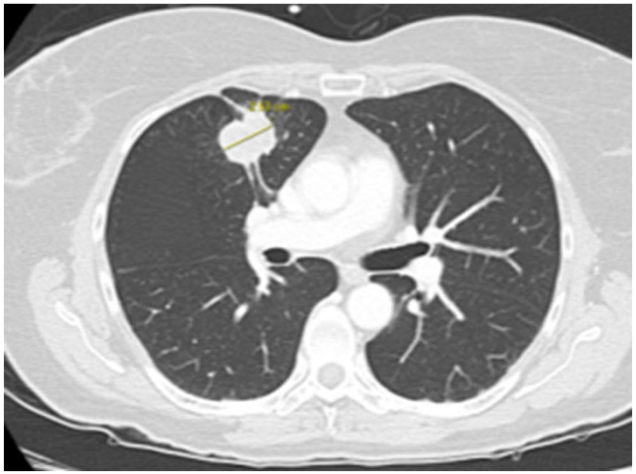
Testing strategy	Cost (CAD$)	QALY	Incremental cost (CAD$)
Liquid biopsy + Tumour tissue biopsy	1,305,524	7.17	Reference
Tumour tissue biopsy alone	1,342,740	7.10	37,216

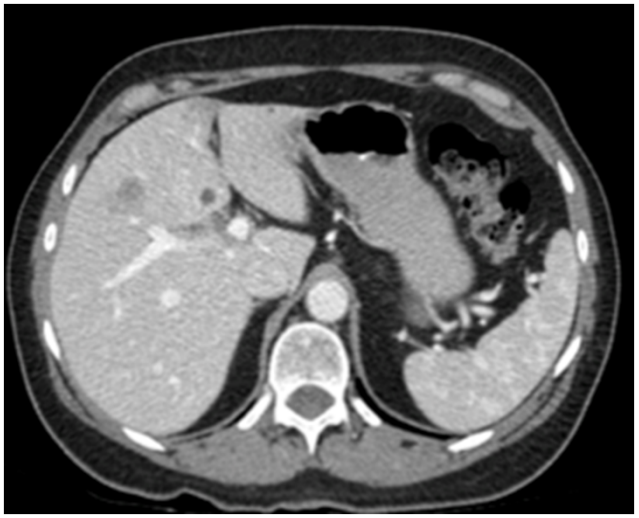
What happened to our patient?

- 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



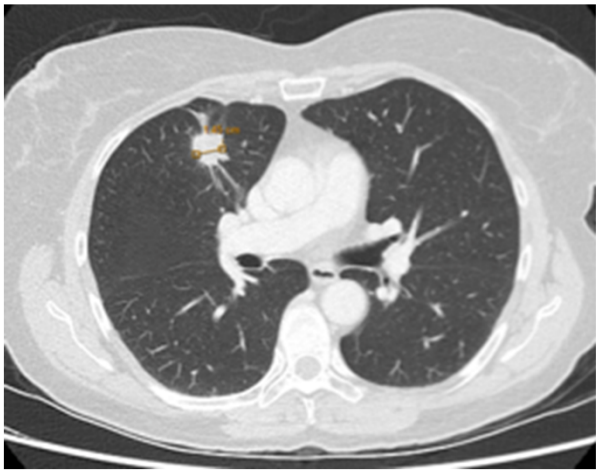
Alteration	% cfDNA or Amp
EGFR E746_A750del (Exon 19 deletion)	2.1%
TP53 N210fs	1.4%

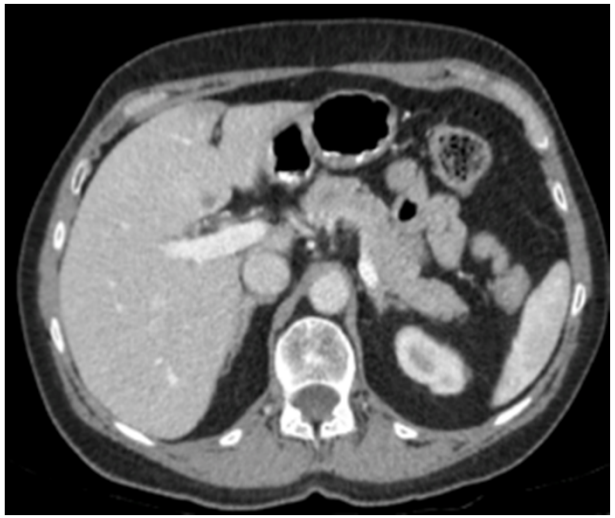




Began osimertinib treatment as part of a targeted therapy trial

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

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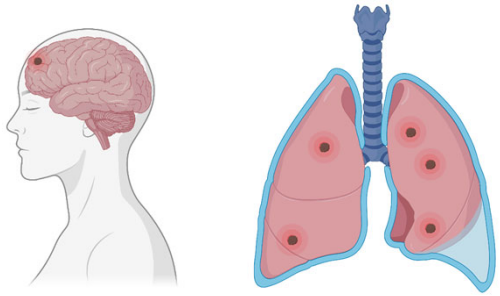
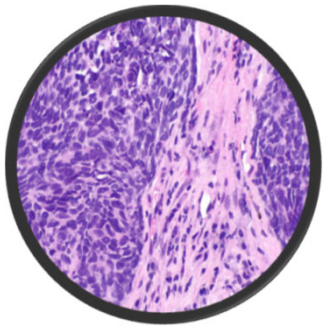
Case presentation

- 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).

cT4 N3 M1c lung adenocarcinoma (stage IVB, AJCC 8th edition).



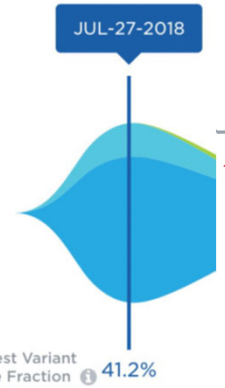


Use of liquid biopsy in advanced NSCLC: When?

- 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

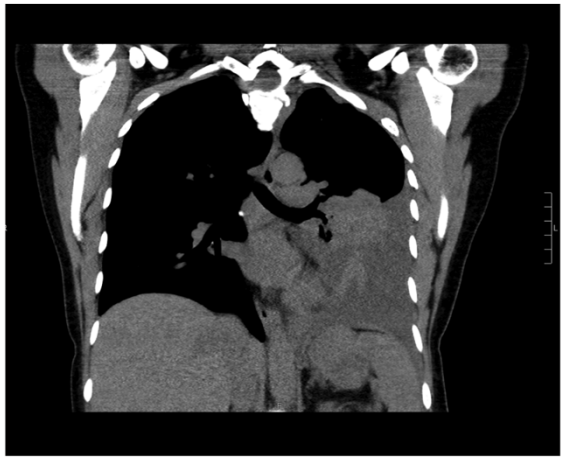
In this case of advanced NSCLC harboring EGFR Exon19del and a small asymptomatic brain metastasis, what would be your choice of therapy?

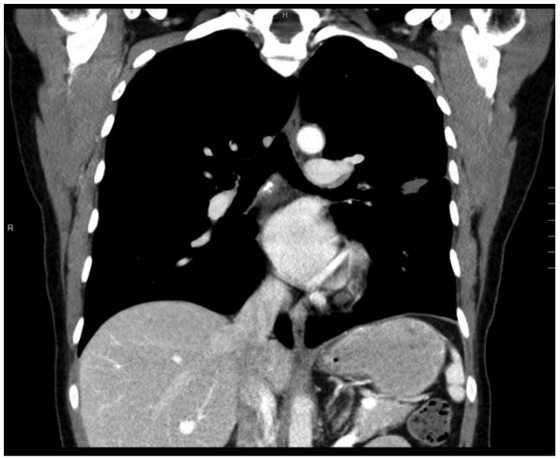
- 1- SBRT to the brain metastasis and start osimertinib
- 2- Osimertinib alone
- 3- EGFR TKI + Bevacizumab
- 4- EGFR TKI + Platinum doublet Chemotherapy



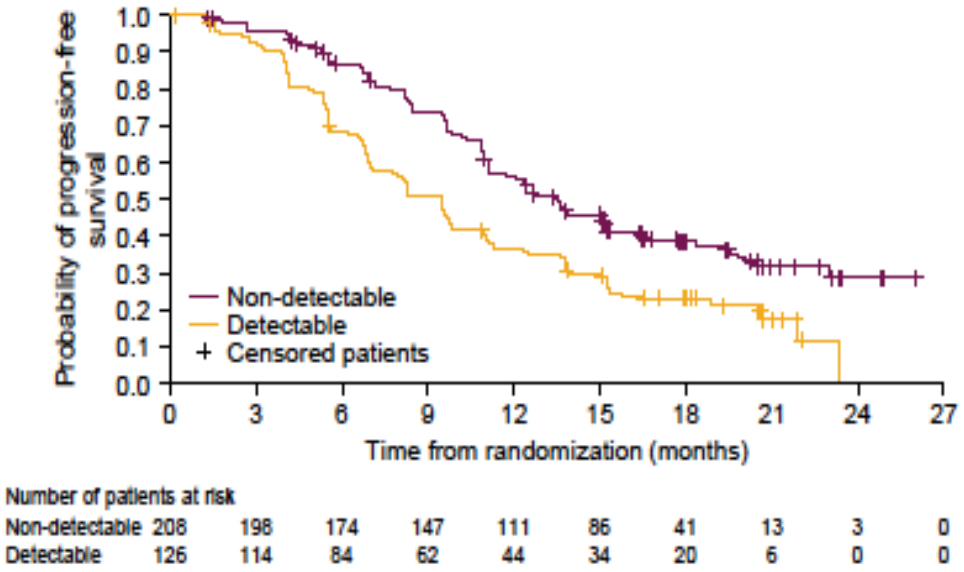
She began osimertinib in August 2018, with an intracranial complete response and extracranial partial response noted

Genetic Alteration	
EGFR E746_A750del	41.2%
EGFR C797S	ND
ARID1A Q456Q	ND
EGFR T790M	ND
TP53 C275Y	ND
ARID1A F1728F	ND
TP53 S127F	6.5%
***BRAF* Amplification**	2.2%
***CDK6* Amplification**	2.2%
***EGFR* Amplification**	3.4%
***NTRK2* L699L**	-
***EGFR* N338N**	ND
***FGFR1* V795I**	ND

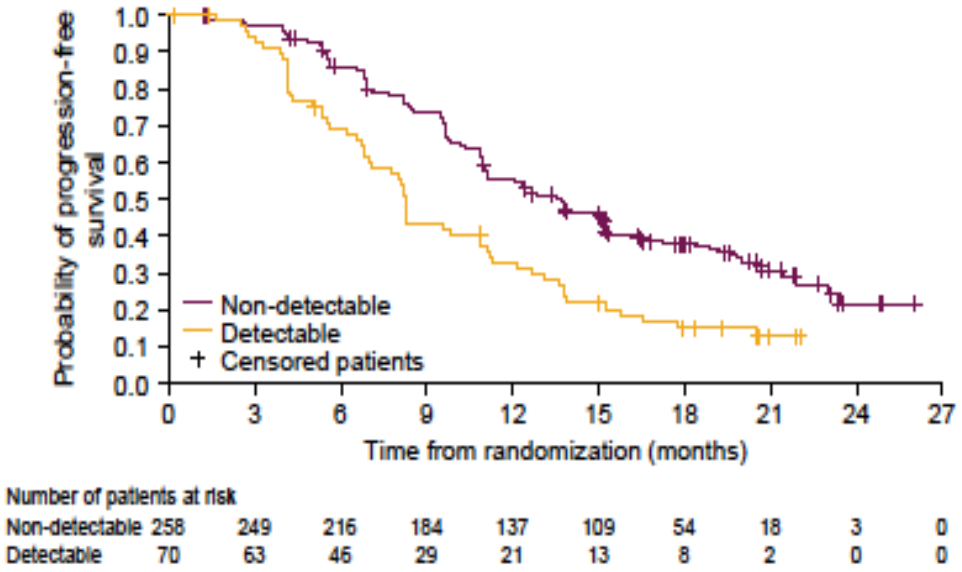




EGFR-mutated NSCLC: FLAURA sub-analysis

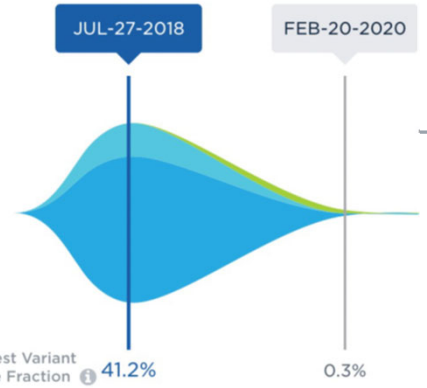


a) Clearance of plasma EGFRm at week 3



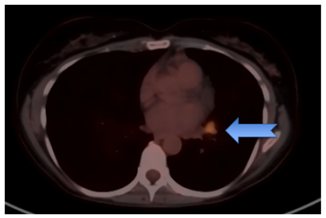
b) Clearance of plasma EGFRm at week 6

Zhou C, et al. ASCO 2019



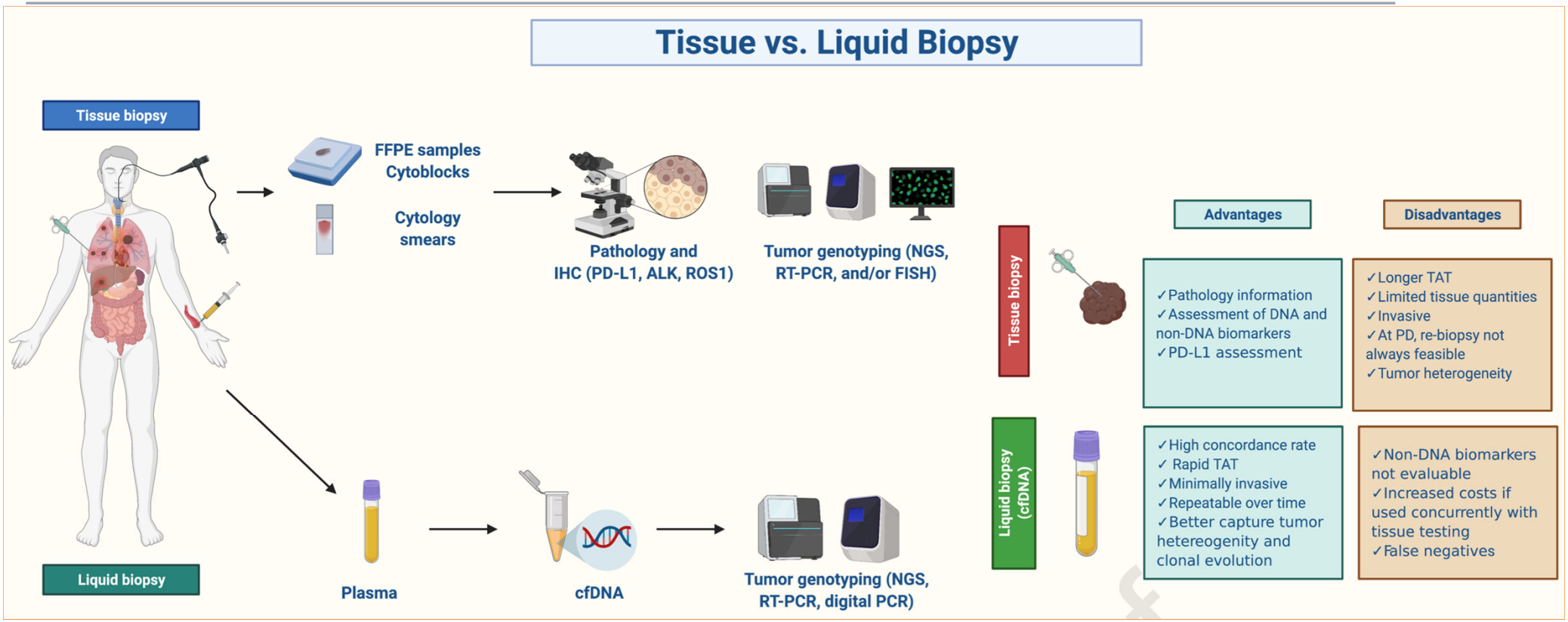
Genetic Alteration		
EGFR E746_A750del	41.2%	0.2%
EGFR C797S	ND	0.3%
ARID1A Q456Q	ND	ND
EGFR T790M	ND	ND
TP53 C275Y	ND	ND
ARID1A F1728F	ND	ND
TP53 S127F	6.5%	ND
BRAF Amplification	2.2%	ND
CDK6 Amplification	2.2%	ND
EGFR Amplification	3.4%	ND
NTRK2 L699L	-	-
EGFR N338N	ND	ND
FGFR1 V795I	ND	ND

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 *EGFR* C797S mutation (0.3% cfDNA).

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

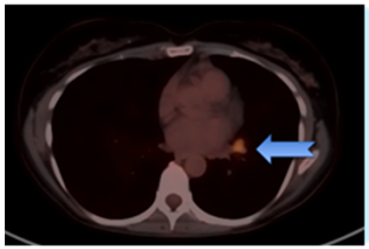


Rolfo et al (Gandara), JTO Oct 2021

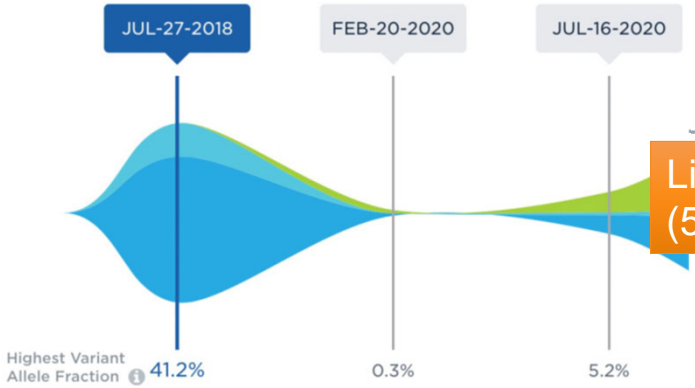
Treatment at Progression

- 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

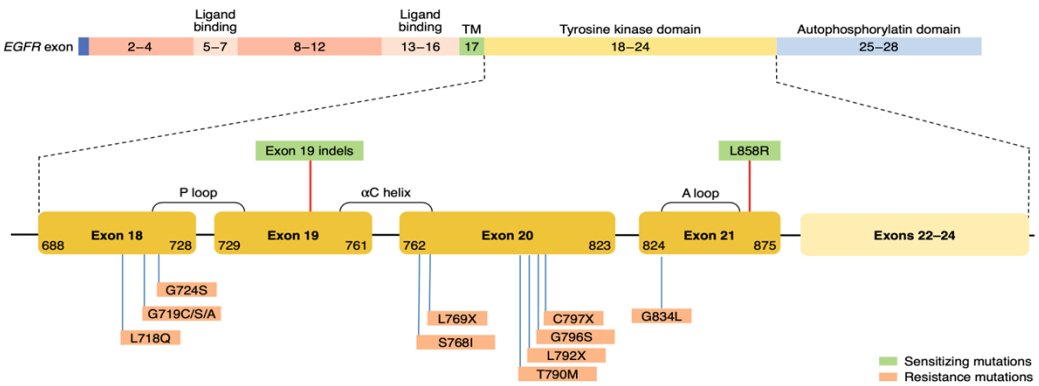


The patient received radiation therapy to the left hilar lymph node, completed in June 2020.
Osimertinib was continued.



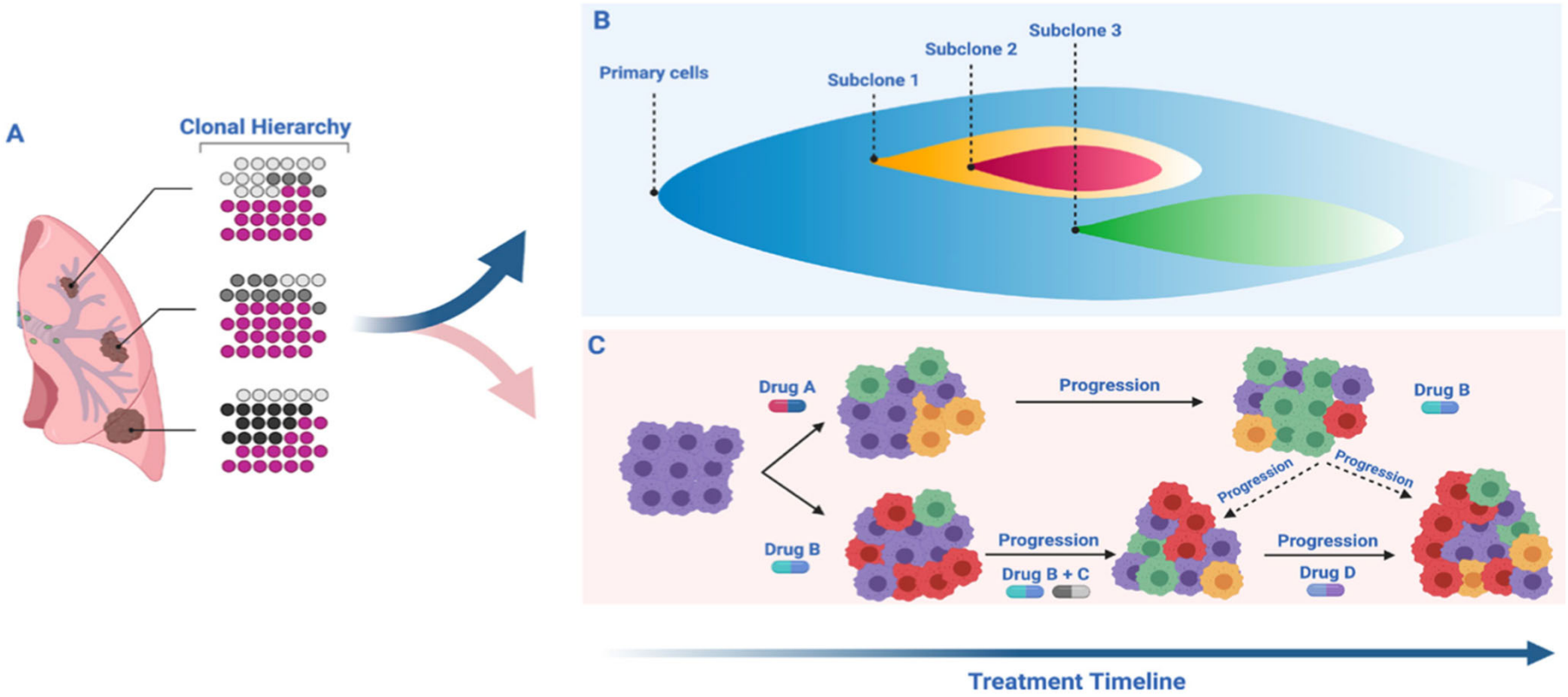
Liquid biopsy in July 2020 showed persistence of *EGFR* C797S (5.2% cfDNA) and *EGFR* exon 19 deletion (4.7% cfDNA) mutations.

Genetic Alteration			
EGFR E746_A750del	41.2%	0.2%	4.7%
EGFR C797S	ND	0.3%	5.2%
ARID1A Q456Q	ND	ND	ND
EGFR T790M	ND	ND	ND
TP53 C275Y	ND	ND	ND
ARID1A F1728F	ND	ND	ND
TP53 S127F	6.5%	ND	0.4%
***BRAF* Amplification**	2.2%	ND	ND
***CDK6* Amplification**	2.2%	ND	ND
***EGFR* Amplification**	3.4%	ND	ND
***NTRK2* L699L**	-	-	-
***EGFR* N338N**	ND	ND	ND
***FGFR1* V795I**	ND	ND	ND



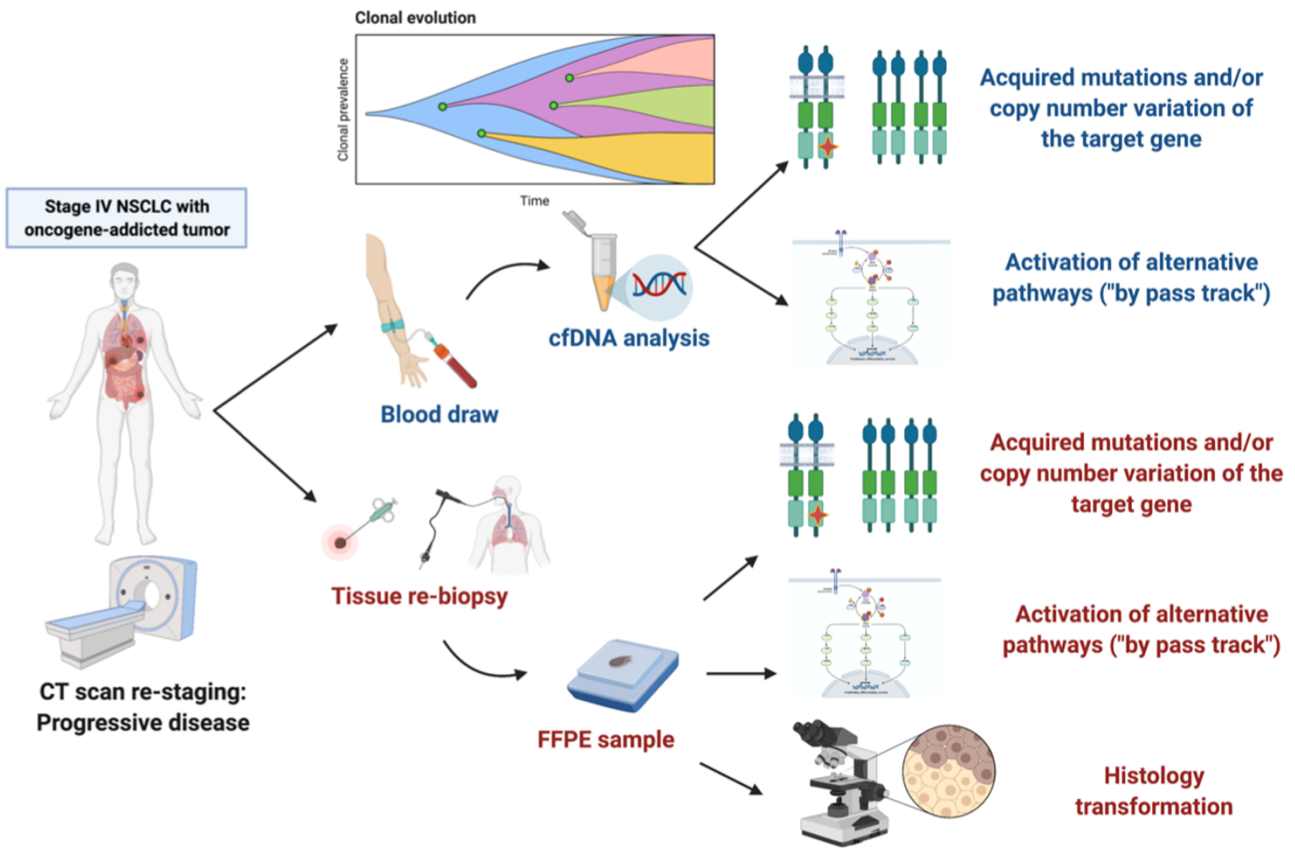
Passaro A., Janne P, Mok T and Peters S. Nature Cancer 2021

Clonal evolution through EGFR Targeted therapy



Passaro A. et al (Rolfo C) ESMO Open 2020

Liquid Biopsy in Acquired Resistance to Targeted Therapy



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

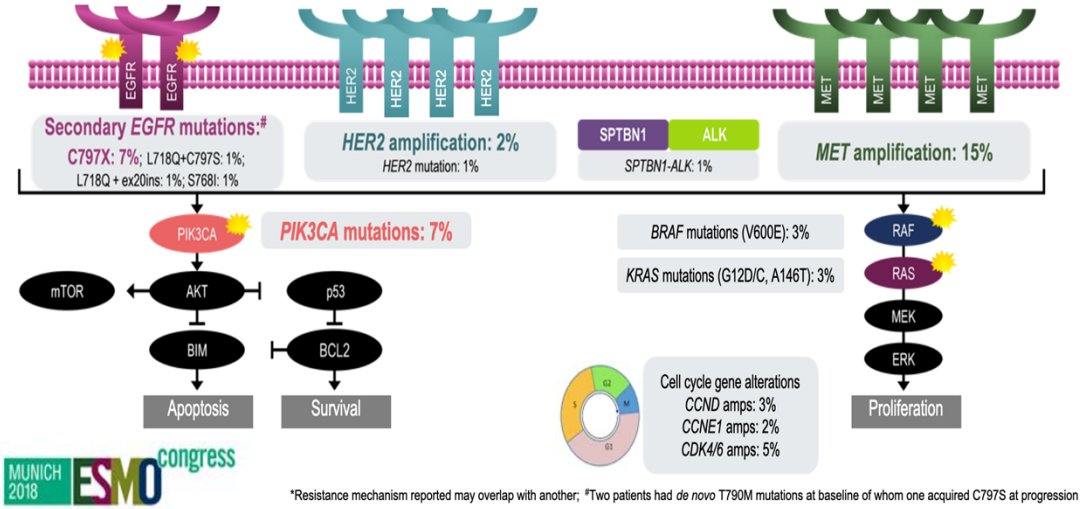
PCR-based approaches:
- ✓Variable sensitivity
- Single/Multiplex gene testing
- Only for mutations

IHC:
- ✓Protein expression

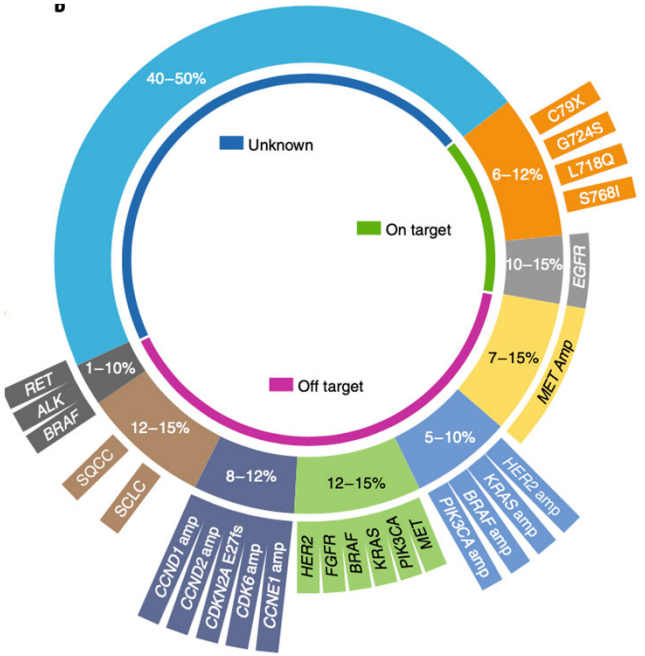
Rolfo et al (Gandara), JTO Oct 2021

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



*Resistance mechanism reported may overlap with another; #Two patients had *de novo* T790M mutations at baseline of whom one acquired C797S at progression

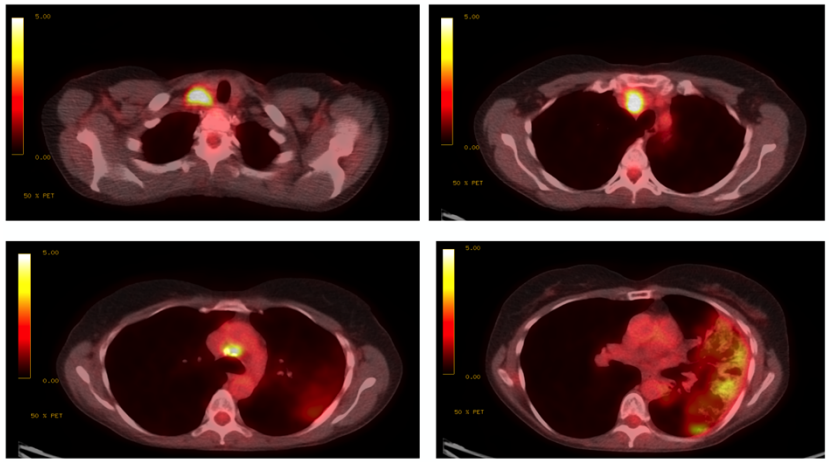


Ramalingam SS, et al. ESMO 2018

Passaro A., Janne P, Mok T and Peters S. Nature Cancer 2021

Genetic Alteration				% cfDNA
EGFR E746_A750del	41.2%	0.2%	4.7%	58.3%
EGFR C797S	ND	0.3%	5.2%	55.6%
ARID1A Q456Q	ND	ND	ND	0.2%
EGFR T790M	ND	ND	ND	ND
TP53 C275Y	ND	ND	ND	ND
ARID1A F1728F	ND	ND	ND	ND
TP53 S127F	6.5%	ND	0.4%	7.6%
***BRAF* Amplification**	2.2%	ND	ND	ND
***CDK6* Amplification**	2.2%	ND	ND	ND
***EGFR* Amplification**	3.4%	ND	ND	4.2%
***NTRK2* L699L**	-	-	-	-
***EGFR* N338N**	ND	ND	ND	ND
***FGFR1* V795I**	ND	ND	ND	ND

PET/CT in August 2020: development of supraclavicular and mediastinal lymphadenopathy plus new bone lesions. Liquid biopsy in August 2020: increasing *EGFR* exon 19 deletion mutation (58.3% cfDNA) and *EGFR* C797S mutation (55.6% cfDNA).



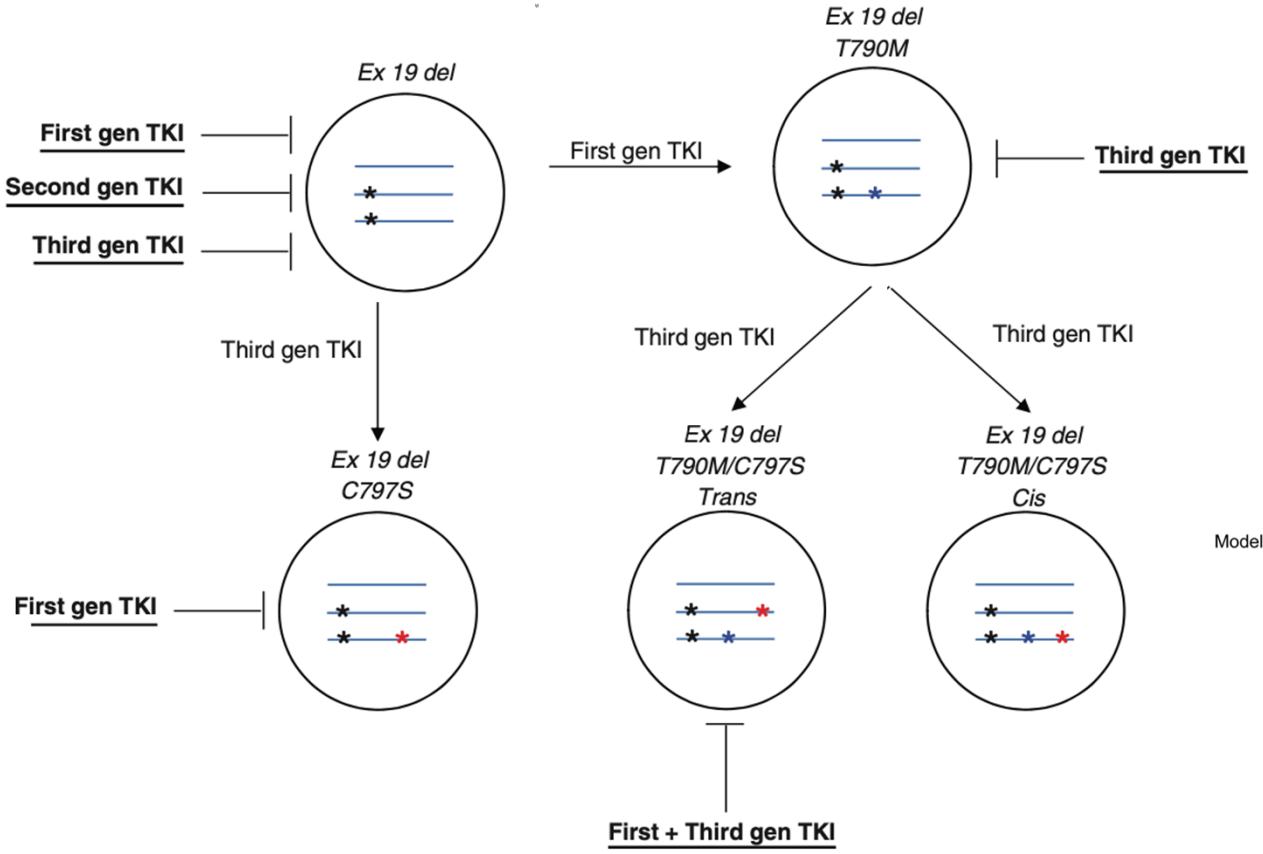
Treatment at Progression

- 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.

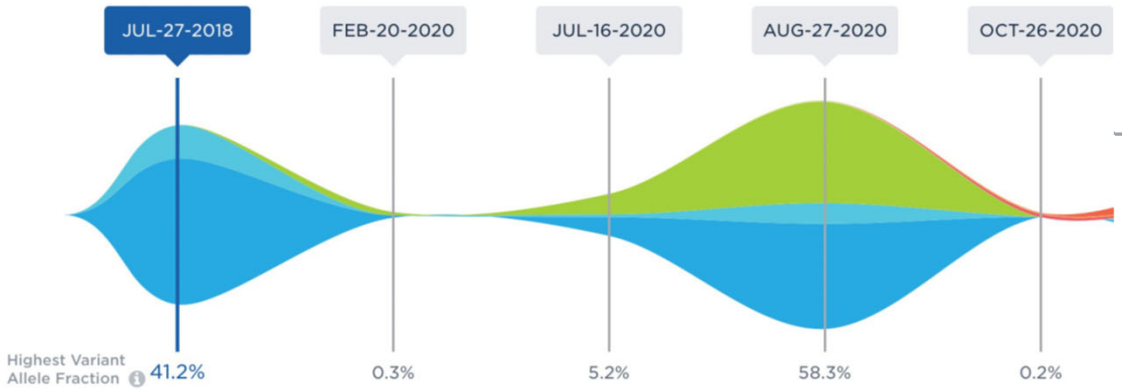


EGFR inhibitor	*EGFR* mutant type (preclinical model prediction)			
	Sensitizing Mutation (SM) exon 19 indels / L858R	SM / C797S	SM / T790M	SM / T790M / C797S
Gefitinib (1st gen. reversible)	sensitive	sensitive	resistant	resistant
Erlotinib (1st gen. reversible)	sensitive	sensitive	resistant	resistant
Afatinib (2nd gen. irreversible)	sensitive	resistant	resistant	resistant
Dacomitinib (2nd gen. irreversible)	sensitive	resistant	resistant	resistant
Osimertinib (3rd gen. irreversible)	sensitive	resistant	sensitive	resistant

Model of sequential use of EGFR inhibitors: **3rd gen. EGFR TKI followed by 1st gen. EGFR TKI**

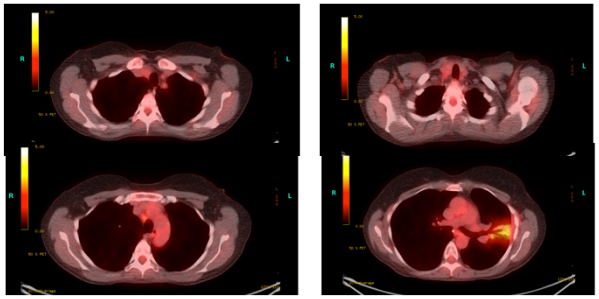
EGFR TKI associated with response	Mechanism of on-target resistance (frequency)	EGFR TKI associated with response (preclinical data)	Mechanism of on-target resistance (frequency)
EGFR-SM	osimertinib → *EGFR*-SM / C797S (? % of cases)	gefitinib / erlotinib	*EGFR*-SM / T790M / C797S (? % of cases)

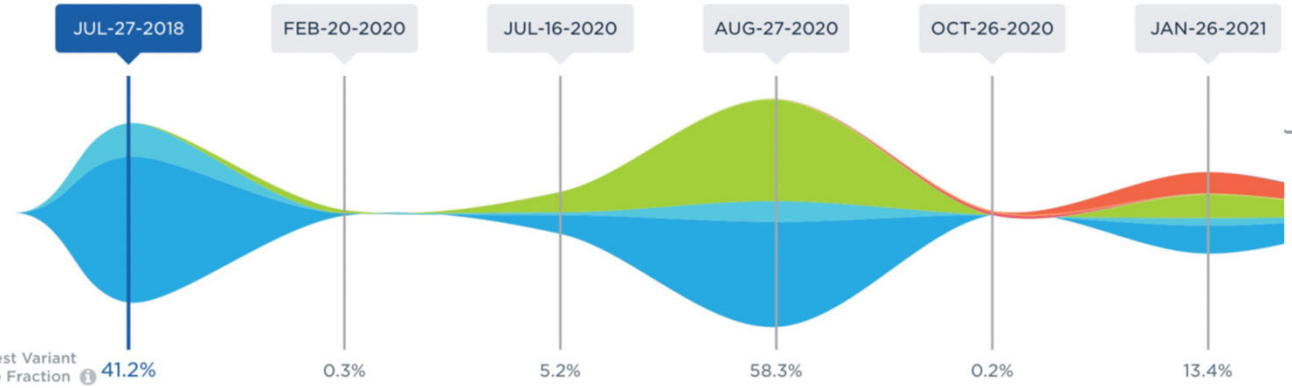
Niederst et al, CCR 2015



Genetic Alteration				% cfDNA or amplification	
EGFR E746_A750del	41.2%	0.2%	4.7%	58.3%	ND
EGFR C797S	ND	0.3%	5.2%	55.6%	ND
ARID1A Q456Q	ND	ND	ND	0.2%	ND
EGFR T790M	ND	ND	ND	ND	ND
TP53 C275Y	ND	ND	ND	ND	ND
ARID1A F1728F	ND	ND	ND	ND	ND
TP53 S127F	6.5%	ND	0.4%	7.6%	ND
***BRAF* Amplification**	2.2%	ND	ND	ND	ND
***CDK6* Amplification**	2.2%	ND	ND	ND	ND
***EGFR* Amplification**	3.4%	ND	ND	4.2%	ND
***NTRK2* L699L**	-	-	-	-	0.2%
***EGFR* N338N**	ND	ND	ND	ND	0.1%
***FGFR1* V795I**	ND	ND	ND	ND	ND

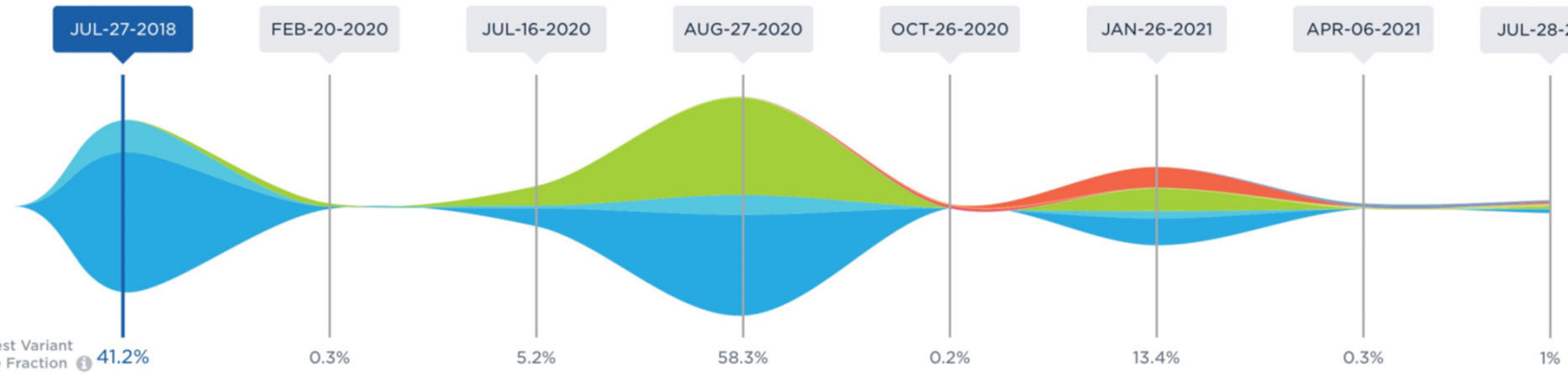
On liquid biopsy collected in October 2020, *EGFR* C797S and *EGFR* exon 19 deletion mutations were not detected. PET/CT in November 2020 showed complete resolution of previously noted intrathoracic lymphadenopathy and no new lesions.





Genetic Alteration	% cfDNA or amplification					
EGFR E746_A750del	41.2%	0.2%	4.7%	58.3%	ND	13.4%
EGFR C797S	ND	0.3%	5.2%	55.6%	ND	10.7%
ARID1A Q456Q	ND	ND	ND	0.2%	ND	0.2%
EGFR T790M	ND	ND	ND	ND	ND	9.6%
TP53 C275Y	ND	ND	ND	ND	ND	ND
ARID1A F1728F	ND	ND	ND	ND	ND	ND
TP53 S127F	6.5%	ND	0.4%	7.6%	ND	2.6%
***BRAF* Amplification**	2.2%	ND	ND	ND	ND	ND
***CDK6* Amplification**	2.2%	ND	ND	ND	ND	ND
***EGFR* Amplification**	3.4%	ND	ND	4.2%	ND	ND
***NTRK2* L699L**	-	-	-	-	0.2%	ND
***EGFR* N338N**	ND	ND	ND	ND	0.1%	ND
***FGFR1* V795I**	ND	ND	ND	ND	ND	ND

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.

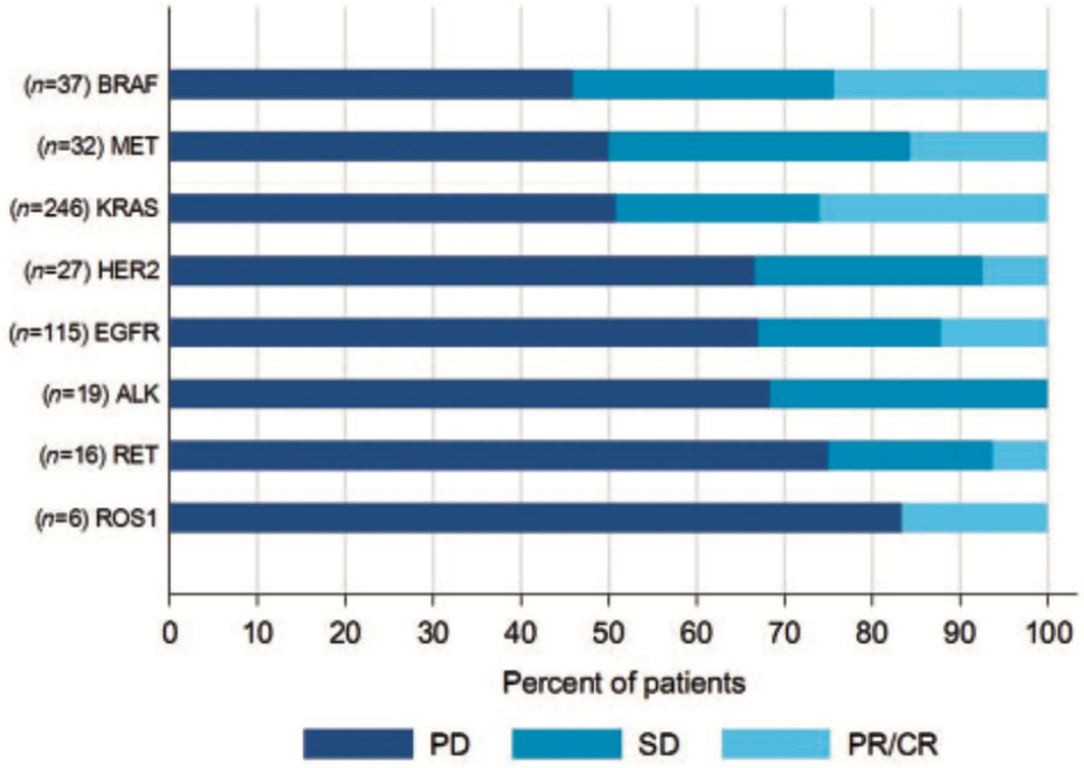


IASLC

Erlotinib was discontinued and she was initiated on chemotherapy with carbo/pemetrexed.

Genetic Alteration	% cfDNA or amplification							
EGFR E746_A750del	41.2%	0.2%	4.7%	58.3%	ND	13.4%	ND	1%
EGFR C797S	ND	0.3%	5.2%	55.6%	ND	10.7%	ND	0.7%
ARID1A Q456Q	ND	ND	ND	0.2%	ND	0.2%	0.3%	0.6%
EGFR T790M	ND	ND	ND	ND	ND	9.6%	ND	0.4%
TP53 C275Y	ND	ND	ND	ND	ND	ND	0.1%	0.2%
ARID1A F1728F	ND	ND	ND	ND	ND	ND	0.3%	0.2%
TP53 S127F	6.5%	ND	0.4%	7.6%	ND	2.6%	ND	0.2%
***BRAF* Amplification**	2.2%	ND	ND	ND	ND	ND	ND	ND
***CDK6* Amplification**	2.2%	ND	ND	ND	ND	ND	ND	ND
***EGFR* Amplification**	3.4%	ND	ND	4.2%	ND	ND	ND	ND
***NTRK2* L699L**	-	-	-	-	0.2%	ND	ND	-
***EGFR* N338N**	ND	ND	ND	ND	0.1%	ND	ND	ND
***FGFR1* V795I**	ND	ND	ND	ND	ND	ND	0.1%	ND

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 acencdotal case!
- Do broad molecular testing on your patients! At least to know the ones will not response to Immunotherapy

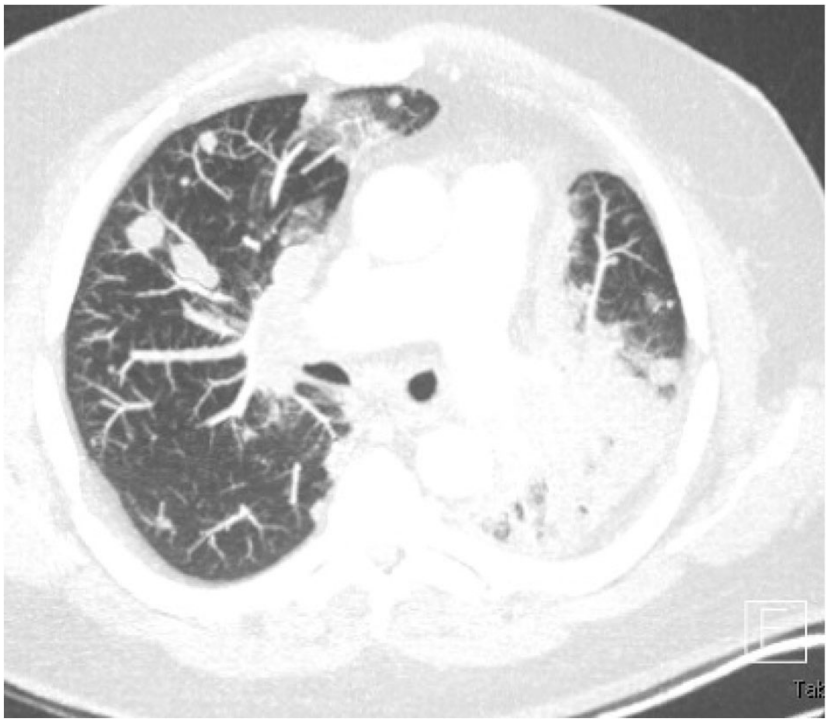
IASLC Liquid Biopsy Webinar: Case #3 in Advanced NSCLC

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

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

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**



Case 3

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).

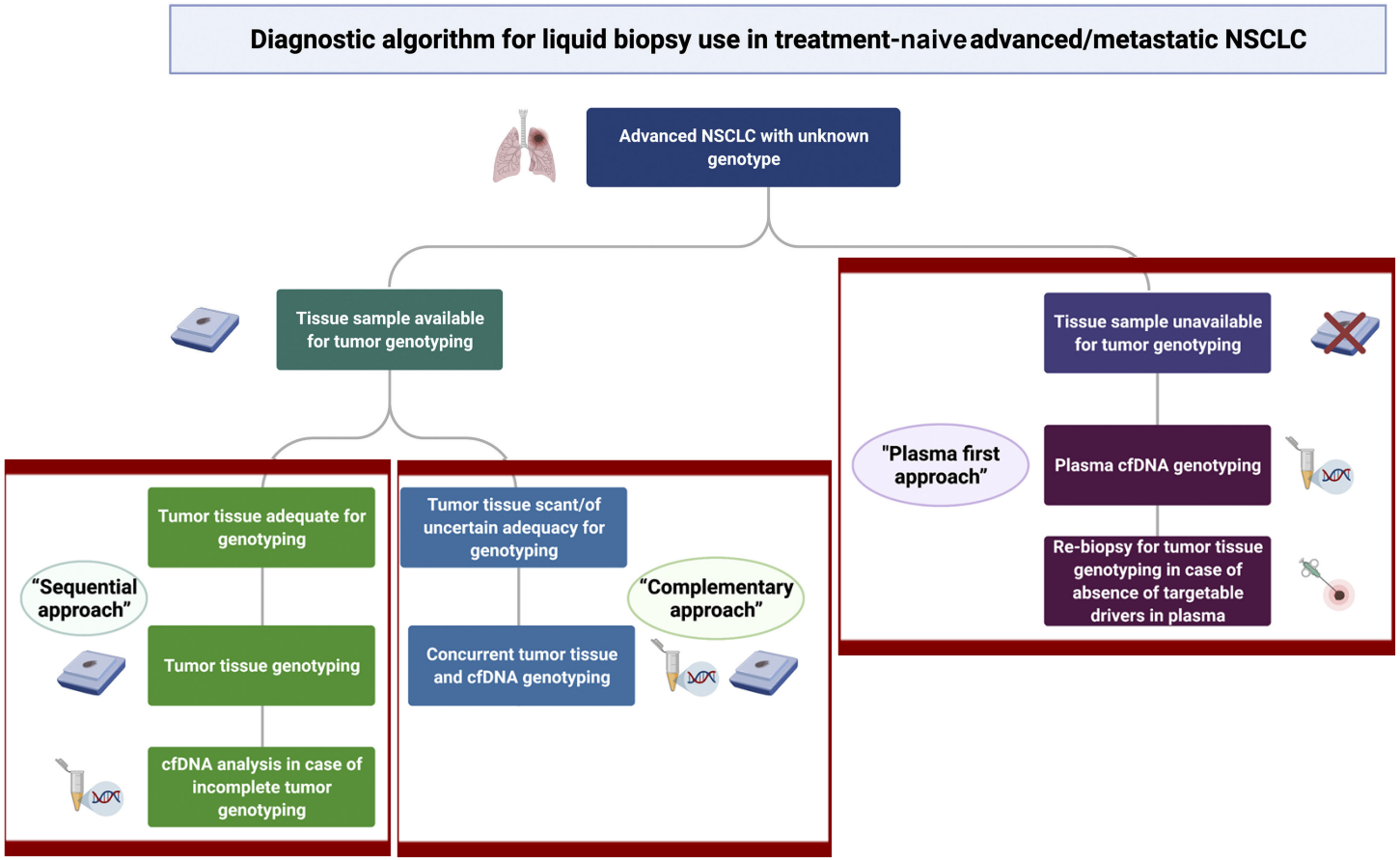
Question 1: How would you proceed with testing, given anticipated turn-around-times (TRT)?

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%.**

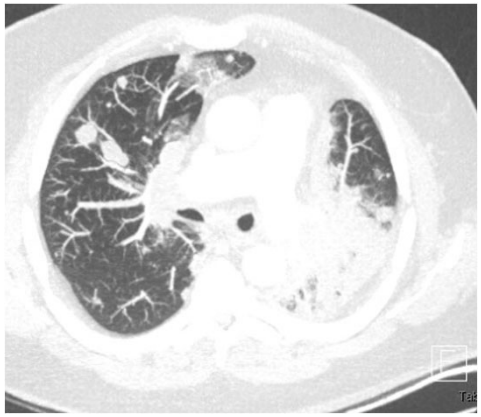
Updated IASLC Consensus Statement on Liquid Biopsy in NSCLC: 2021



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							
Study	**Drug (vs Chemo)**	**PDL1 Selection**	**Line of Tx**	**Control**	**Primary Endpoint**	**HR-Primary Endpoint**	**Result**
KN024	Pembro	≥50%	1st	Plat Chemo	PFS	0.50	Positive
CM026	Nivo	≥5%	1st	Plat Chemo	PFS	1.15	Negative
MYSTIC	Durva or Durva-Tremi	≥25%	1st	Plat Chemo	PFS & OS	NR	Negative
KN189 (Non-SQ)	Pembro-Chemo	≥1%	1st	Plat Chemo	PFS	0.52	Positive
KN042	Pembro	≥1%	1st	Plat Chemo	OS	0.81 for OS 0.69 for 50%	Positive
KN047 (SQ)	Pembro-Chemo	None	1st	Plat-Nab Paclitaxel	PFS & OS	0.64 for OS	Positive
Impower 150 (Non-SQ)	Atezo +Bev/ Pac/Carbo	None	1st	Bev/Pac Carbo	PFS OS	0.71	Positive
Impower 131 (SQ)	Atezo + Nab/Carbo	None	1st	Pac/Carbo	PFS,OS	0.71 (PFS)	Positive
CM227	Nivo or Nivo-Ipi	<1%/1% & TMB≥10	1st	Plat Chemo	PFS & OS	0.58 (in H-TMB)	Positive
IMpower 110	Atezo	≥1%	1st	Plat Chemo	OS in TC3/IC3	0.59	Positive
CM-9LA	Nivo-Ipi-Chemo	None	1st	Plat Chemo	OS	0.66	Positive
EMPOWER-lung1	Cemiplimab	≥50%	1st	Plat Chemo	OS,PFS	0.57	Positive

Adapted from Gandara: ELCC 2021

Parameters

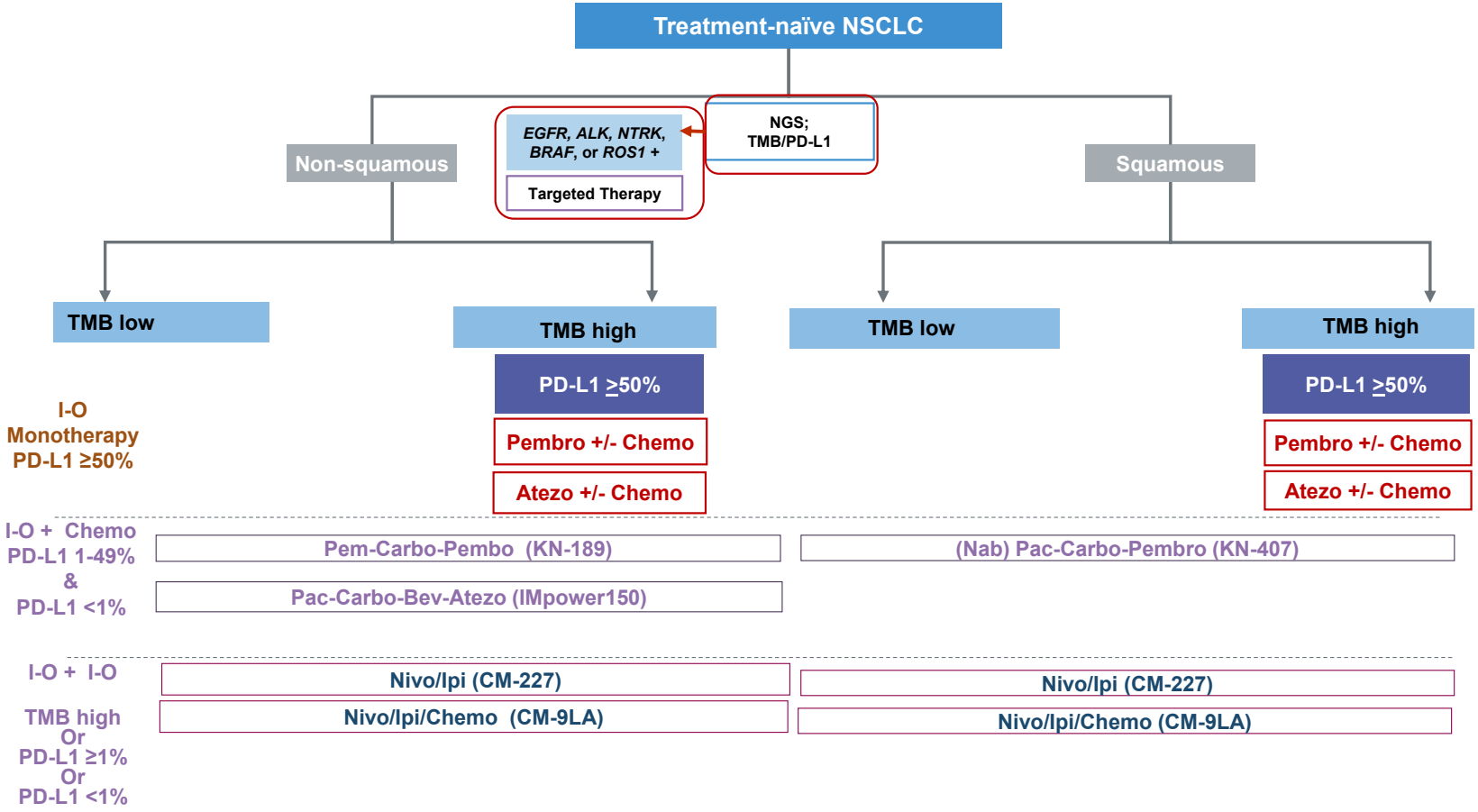
Test Regimen
CPI Monotherapy
CPI+Chemo
CPI+Chemo+Bev
CPI + CTLA4

Biomarker
None
PD-L1
TMB

Histology
All
Squamous
Non-Squamous

Primary Endpoint
PFS
OS
Both

Stage IV NSCLC: Biomarker-driven Therapeutic Landscape Algorithm



Gandara ELCC 2021. (Adapted from S Peters: ILCC 2020)

CodeBreak100: Phase 2 Trial of Sotorasib in *KRAS*p.G12C NSCLC

clinicaltrials.gov identifier: NCT03600883

Screening / Enrollment

Key Eligibility:

- Locally advanced or metastatic NSCLC
- *KRAS* p.G12C mutation as assessed by central testing of tumor biopsies
- Progressed on prior standard therapies[a]
- No active brain metastases

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)

Safety and Long-term Follow-up[c]

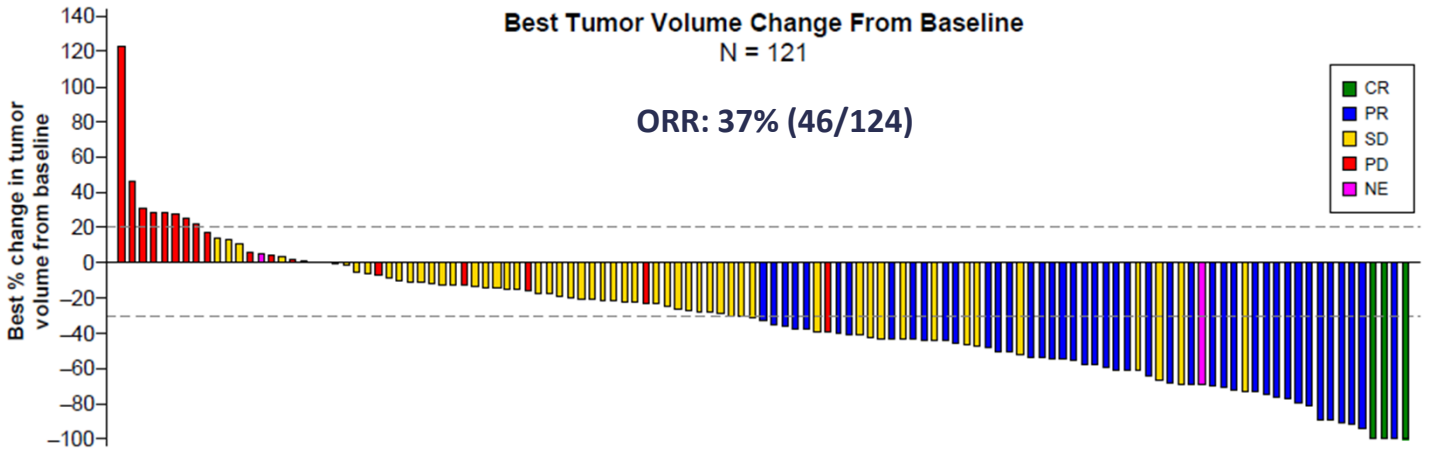
a: no more than 3 prior lines of therapies were allowed; b: treatment beyond disease progression was allowed if certain criteria were met; c: safety follow-up occurs 30 (+7) days after the last dose of sotorasib; long-term follow-up occurs every 12 (±2) weeks for up to 3 years.
NSCLC: non-small cell lung cancer; ORR: objective response rate; DoR: duration of response; TTR: time to response; PFS: progression-free survival; OS: overall survival; PD-L1: programmed death-ligand 1; RECIST: Response Evaluation Criteria in Solid Tumors.

Li BT et al. WCLC 2020. Abstract PS02.07

CodeBreak100: Depth of Tumor Response

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%



Graph excluded 3 patients without post-baseline measurement in target lesions.
CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NE: not evaluable.

IASLC 2020 World Conference on Lung Cancer Singapore

Li BT et al. WCLC 2020. Abstract PS02.07

Case 3

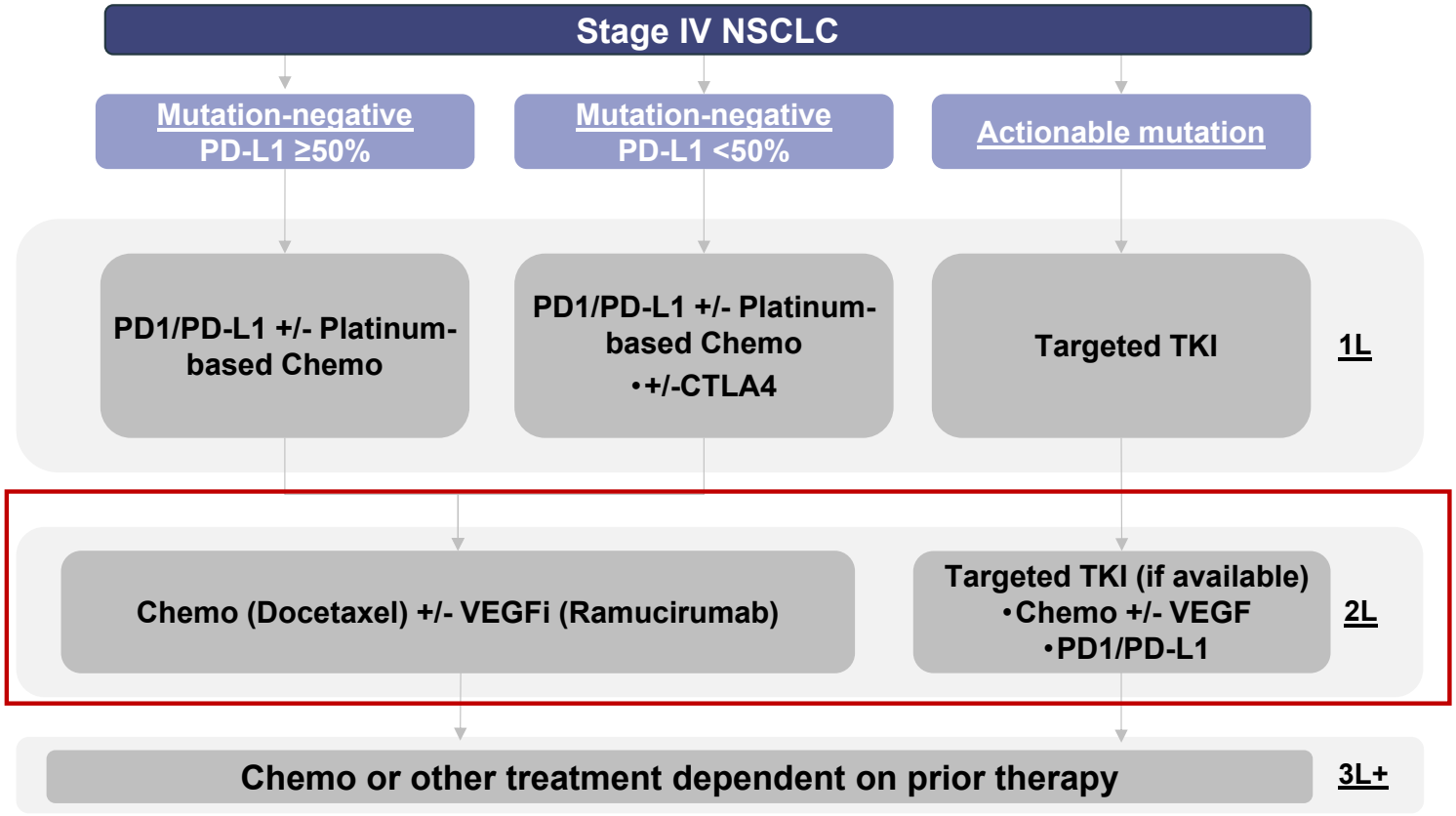
The patient is treated with pemetrexed/carboplatin/pembrolizumab & achieves a partial response.

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%:

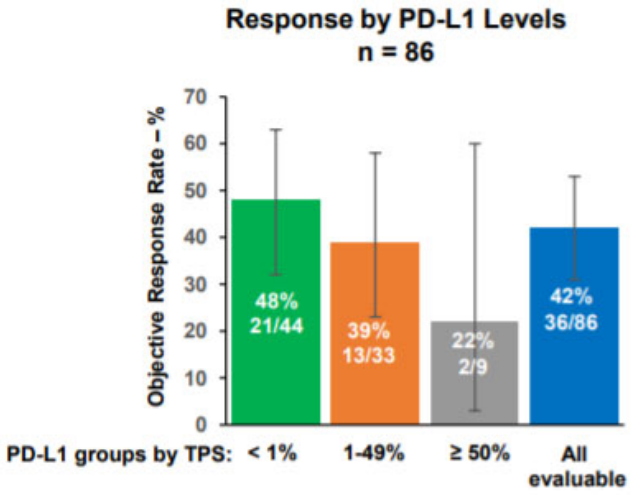
Question 3: Which do you recommend for at this point?

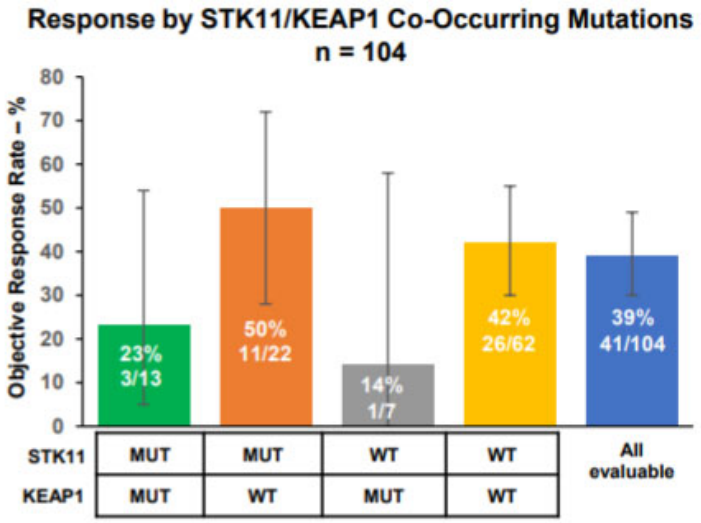
1. **SBRT to all sites of PD & continue pemetrexed & pembrolizumab maintenance therapy.**
2. **Switch to sotorasib (AMG510).**
3. **Switch to docetaxel/ramucirumab.**
4. **Switch to nivolumab/ipilimumab.**

Current Stage IV NSCLC Treatment Paradigm: 1st→ 2nd→ 3rd Line Therapy



Tumor Response by PD-L1 Levels & STK11/KEAP1 Co-Occurring Mutations



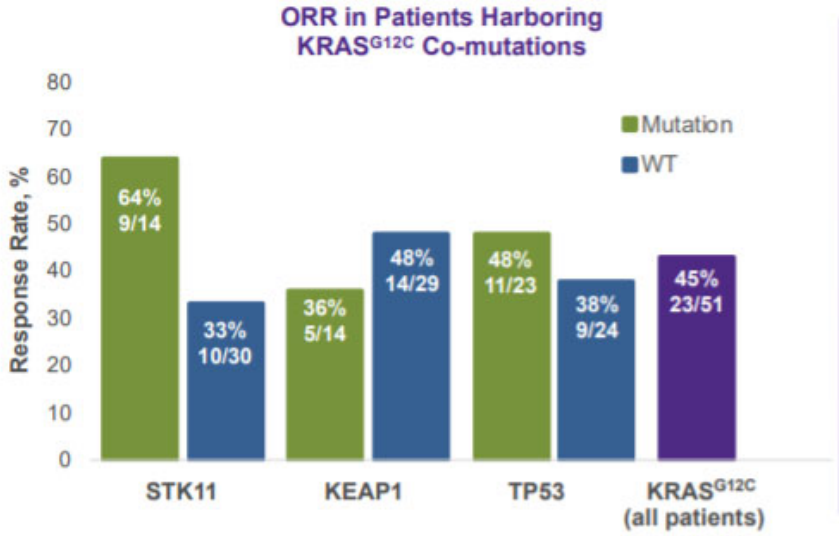


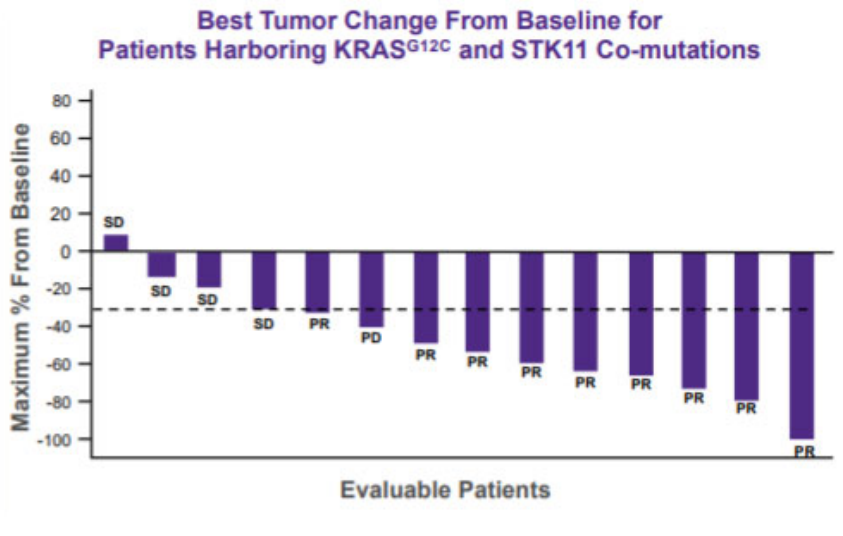
Li et al. *WCLC* 2020

IASLC 2021 Targeted Therapies of Lung Cancer Meeting
FEBRUARY 17 – 21, 2021 | WORLDWIDE VIRTUAL EVENT

- 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





- Baseline NGS reports reviewed for exploratory correlative analysis for all NSCLC patients with available mutation data[a]
- **64% ORR** in patients with tumors harboring STK11 and KRASG12C mutations
- No apparent trend with KEAP1, TP53, or other common mutations and response rate

[a]Analysis includes key mutations detected at baseline in tumor and/or plasma that commonly occur with KRASG12C. Mutations included as positive include, nonsense, frameshift, splice site, and recurrent mutations predicted to have deleterious impact, and excluded VUS.
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